Schizophrenia:
Neuronal correlates of self-disturbance and neurocognitive impairments as potential predictors for psychosis risk.

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I Summary

Schizophrenia is a severe mental disorder characterized by an often devastating course leading to disability and to substantial costs for the mental health system. In recent years, an increased interest in the early phase of schizophrenia and other psychotic disorders has emerged. This is due to several reasons. Foremost, early signs of the illness are rather non-specific and develop in a subtle manner and as a result, there is often a substantial delay until a diagnosis is specified and therapies will be initiated. Then, already in the prodrome, a combination of agonizing symptoms, associated neurocognitive deficits, educational crisis and a loss of social embedment may lead to a downward spiral. The only young individuals may lose the chance for rehabilitation after recovery from the illness. A long duration of untreated prodrome and psychosis has further been linked to more negative outcomes. Subsequently, prospective studies demonstrated that in many cases early detection of the disorder is possible. Today it is accepted, that early intervention and prevention strategies may enhance the course and the prognosis of the disorder. However, the identification of a prodrome and of "true positive" individuals at risk for psychosis has proven to be challenging. Besides, the identification and treatment of "false positive" may produce unnecessarily self-perceived stigma and discrimination. Research related to early detection therefore tries to optimize the prediction accuracy in risk assessments by including different measurements of putative biological or trait markers of underlying vulnerability to psychosis.

Ego-pathology symptoms seen in schizophrenia are often denotated as Schneiderian first-rank symptoms and are thought to contain a high positive predictive value for the disorder. Theoretical and empirical work indicates that the self-disturbance in schizophrenia occurs on a basic pre-reflective level, while affecting additionally higher cognitive processes. Neurocognitive research has shown that on the one hand, source or self-monitoring deficits may particularly contribute to disturbances in the feeling of ownership. On the other hand, aberrant salience and associated disturbances of memory and attention processes may contribute to hyper-reflexivity and to a failure in intuitive social understanding. Only recently it has been suggested that a subtle self-disturbance is already present in the prodrome and may serve as marker, helping to optimize the prediction of who is truly at-risk.

The neurodevelopmental model of schizophrenia assumes a genetic-biological determined vulnerability that is associated with neurocognitive impairments that are detectable before the initial onset of the illness. Studies on at-risk psychosis individuals matched with healthy controls found small to medium impairments across most neurocognitive domains in at-risk subjects that are at intermediate level between that of healthy individuals and those diagnosed with schizophrenia. At-risk individuals who later converted to psychosis exhibited more severe neurocognitive deficits at baseline than non-converter in almost all domains, but especially in the domains of speed, verbal fluency and memory. However, due to methodological issues the findings were often inconsistent. Furthermore,

only few studies have addressed the appearance of deficits in an early (High-Risk) and late at-risk (Ultra-High-Risk) state so far.

The purpose of the present work was to contribute to both, research related self-disturbance and neurocognitive impairments as possible marker of psychotic vulnerability.

Study I, entitled "Evaluation of trait adjectives and ego pathology in schizophrenia: an N400 study" emphasized on manifest ego-pathology symptoms in schizophrenia to explore whether N400 related alterations may comprise useful measurements for future at-risk assessments. The N400 event-related potential is evoked by any potentially meaningful stimulus and is thereby meant to reflect semantic processing of information. An alteration of the N400 in patients suffering from schizophrenia has been repeatedly reported and was found to be linked to an abnormal activation of the semantic memory associative networks and presumably to weakening of contextual constraint causing integration deficits. To study the network and organization of self-related reflective memory a study paradigm was implicated that has been shown before to engage subjects in self-referential mental activity. More precisely, schizophrenia patients and healthy controls viewed sequentially presented trait-adjectives and indicated whether or not trait adjectives applied to themselves, or another person. The aim was to explore whether an altered N400 may be found in semantic violations of the own self-concept and how it is associated with underlying ego-pathology in schizophrenia. The data yielded that in healthy controls a classic N400 effect can be induced by processing of trait adjective incongruent with the own self-concept. Additionally, a bias to faster reaction time judging the appropriateness of the trait adjectives in the self- compared to the other-reference condition was observed. Neither the N400 effect nor the reaction-time advantage in self-reference trials could be detected in the schizophrenia group. The integration and inhibition theory of the N400 may explain the missing N400 effect in patients whereas the behavioural data may additionally support the assumption of impaired semantic memory associative networks. Furthermore, the severity of ego-pathology in schizophrenia was correlated with the strength of the N400 effect, which may reflect a missing "internal prime" of a stable self-concept

In **study II**, entitled "Neurocognitive profiles in help-seeking individuals: Comparison of risk for psychosis and bipolar disorder criteria" established neurocognitive tests were used to explore the cognitive profile of help-seeking individuals exhibiting subthreshold psychotic symptoms and participating at the prospective longitudinal and multidimensional early detection study ZInEP (Zurich Program for sustainable Development of Mental Health Services). Study II aims to investigate whether neurocognitive measures are sensitive enough to differentiate between an early (High-Risk, HR) and late (Ultra High-Risk, UHR) prodromal state and further, aims to examine the demarcation to a bipolar disorder risk state (HRBip). The results revealed foremost, that, in line with previous literature, the three at-risk groups were impaired relative to the control group on all domains in the

way that the HR and HRBip were performing both at comparable and at an level between controls and UHR. Further, among subjects at-risk of schizophrenic psychosis, performance in speed domain predicted a group affiliation of UHR while learning and memory deficits predicted a conversion to psychosis. Our data is in line with previous research and suggests processing speed as a central deficit associated with risk for psychosis. The observed poor results in the learning and memory domain in subjects who later converted to psychosis may indicate early functional degenerative processes. However, we found no putative prodrome features that clearly distinguished between the early HR and the at-risk bipolar state. We assume that in these early stages, potential impairments associated with psychotic vulnerability might have been too subtle and therefore overlain by other attributes associated with the HR state. Overall, we found that in all at-risk subjects neuropsychological deficits had a profound effect on level of general functioning and general satisfaction with life.

Studying the appearance of symptoms in a putative at-risk state of psychosis appears to be promising because confounding effects of ongoing illness, treatment and other complications may be avoided. At the end, it contributes to the understanding of the pathophysiological changes that must occur with the development of psychosis.

II Zusammenfassung

Die Schizophrenie ist eine schwere psychische Störung, die weltweit mit einer Lebenszeitprävalenz von etwa einem Prozent auftritt. Sie ist durch einen variablen Krankheitsverlauf gekennzeichnet und kann bei chronischem Verlauf hohe Gesundheitskosten verursachen. In den letzten Jahren ist das Interesse an der Früherkennung und Frühbehandlung der Schizophrenie und anderen psychotischen Störungen stetig gestiegen. Dies wurde durch verschiedene Erkenntnisse ausgelöst. Erstens, die Schizophrenie entwickelt sich schleichend mit unspezifischen Frühsymptomen, weswegen häufig viel Zeit verstreicht bis eine korrekte Diagnose gestellt und Therapien initiiert werden. Zweitens, bereits in dieser unspezifischen Frühphase der Krankheit (dem Prodrom), also bevor akut psychotische Symptome auftreten, kann die Kombination von quälenden unterschwelligen Symptomen sowie neurokognitiven Funktionseinbussen einen Leistungsabfall verursachen. Die damit verbundenen Probleme in der Ausbildung, im Aufrechterhalten einer Berufstätigkeit oder in der Einbettung im sozialen Kontext können zu einer Abwärtsspirale führen. Dadurch verlieren die bei einem durchschnittlichen Ersterkrankungsalter von 18 bis 25 Jahren noch sehr jungen Erwachsenen bereits dann die Chancen auf eine gute Rehabilitation nach Erholung von der Krankheit. Die Länge der Dauer einer unbehandelten Psychose wurde desweiteren mit einem schlechteren Ausgang und Verlauf der Krankheit in Zusammenhang gebracht. Prospektive Studien zeigten schliesslich auf, dass in vielen Fällen eine Früherkennung der Störung möglich ist. Es ist heute weithin akzeptiert, dass eine frühe Intervention sowie Strategien zur Prävention den Verlauf und die Prognose günstig beeinflussen können. Die Identifikation eines Prodroms, das heisst, von „richtig positiv“ eingestuften Individuen mit tatsächlichem Psychoserisiko, gestaltet sich jedoch äusserst schwierig. Die Behandlung von fälschlicherweise als Risikopatienten eingestuften Personen andererseits kann unnötige Stigmatisierung und Diskriminierung auslösen. Übergeordnetes Ziel im Bereich der Forschung um die Früherkennung von Psychosen ist es daher, die Vorhersagegenauigkeit in den Risikoassessments zu erhöhen. Dies soll ermöglicht werden, indem zusätzliche Informationen von biologischen und anderen charakteristischen Markern der Psychosevulnerablität in die Assessments mit einbezogen werden.

Die psychopathologische Symptomgruppe der „Ich-Störungen“, auch Schneider’s Erstrangsymptome genannt, soll einen hohen positiv prädiktiven Vorhersagewert für die Schizophrenie beinhalten. Theoretische und empirische Studien zeigen auf, dass in der Schizophrenie Selbst-bezogene Prozesse bereits auf einem frühen, präreflektiven Niveau gestört sein können, was sich in der Folge auch auf höhere kognitive Prozesse auswirken kann. Neurowissenschaftliche Studien lassen vermuten, dass einerseits Ausfälle des „source- oder self-monitoring“ Systems ein gestörtes Gefühl der Meinigkeit („sense of ownership“) verursachen können. Eine fehlerhafte Bewertung von Kontext und Umgebungsreizen („aberrant salience“) kann andererseits Einbussen der Aufmerksamkeit und der Gedächtnisfunktionen bewirken. Beides soll zu einem Zustand der „Hyperreflexivität“ führen, sowie

zu einem verminderten Verständnis des intuitiven sozialen Kontexts. Erst kürzlich wurde festgehalten, dass subtile Veränderungen der Selbst-Wahrnehmung bereits im Prodrom einer Psychose auftreten können. Deren Identifikation im diagnostischen Prozess sollte die Vorhersagegenauigkeit erhöhen.

Neurobiologische Erklärungsmodelle der Schizophrenie gehen von einer multifaktoriell bedingten Entwicklungsstörung des Gehirns aus. Diese kann neurokognitive Einbussen verursachen, die bereits früh auftreten und die bereits vor der Erstmanifestation der Krankheit nachweisbar sind. Studien zeigten, dass Individuen mit einem Psychoserisiko, verglichen mit Gesunden Kontrollpersonen, leichte bis mittelschwere Defizite innerhalb der meisten neurokognitiven Domänen aufwiesen. Diese lagen auf einem Niveau zwischen demjenigen von Gesunden und demjenigen von Individuen mit diagnostizierter Schizophrenie. Risikoprobanden, die später eine Psychose entwickelten waren in der Initialuntersuchung schwerer beeinträchtigt als Risikoprobanden, die keine entwickelten, und zwar insbesondere in den Bereichen Verarbeitungsgeschwindigkeit, Wortflüssigkeit und Gedächtnis. Die Erkenntnisse in dem Bereich sind jedoch immer noch uneinheitlich und die Studien aus methodologischen Gründen schwer miteinander vergleichbar. Bis jetzt haben sich erst wenige Studien den Erscheinungsformen der Defizite in frühen (High-Risk) und späten (Ultra-High-Risk) Stadien gewidmet. Ziel der vorliegenden Arbeit war es, einen Beitrag zur Erforschung dieser beiden Marker der Psychosevulnerabilität zu leisten: zur gestörter Selbst-Wahrnehmung sowie zu neurokognitiven Defiziten.

Die **Studie I**, mit dem Titel „Evaluation of trait adjectives and ego pathology in schizophrenia: an N400 study“ hatte zum Ziel, die manifeste Symptomatik der Ich-Störung in Patienten mit Schizophrenie anhand von Veränderungen im ereigniskorrelierten Potential N400 zu untersuchen. Die N400 wird durch jeden potentiell bedeutungsvollen Stimulus ausgelöst und spiegelt die semantische Verarbeitung von Information. Eine Veränderung der N400 in Patienten mit Schizophrenie wurde wiederholt berichtet und mit gestörter Aktivierung des assoziativen semantischen Gedächtnisses in Verbindung gebracht. Um das Netzwerk und die Organisation des Selbst-referentiellen reflektiven Gedächtnisses zu untersuchen, wurde ein experimenteller Versuchsaufbau erstellt, in welchem die Probanden in selbst-bezogene mentale Kognitionen involviert wurden. Patienten und gesunde Kontrollpersonen lasen fortlaufend präsentierte Eigenschaftswörter und beurteilten, ob diese sie selbst, oder eine ihnen gut bekannte Person beschreiben. Es wurde dabei untersucht, ob die N400 durch nicht-zutreffende, und daher das semantische Selbst-Konzept verletzende, Eigenschaftswörter ausgelöst werden kann. Zudem wurde untersucht, ob dabei ein Zusammenhang mit dem Schweregrad der Ich-Störung der Patienten nachweisbar ist. Die Ergebnisse beinhalteten, dass bei gesunden Kontrollpersonen tatsächlich ein klassischer N400-Effekt durch die inkongruenten Eigenschaftswörter ausgelöst werden kann. Bei den Gesunden zeigte sich desweiteren eine Tendenz zu schnelleren Reaktionszeiten in der Selbst- verglichen mit der Andere-Bedingung. Der N400-Effekt sowie der

Reaktionszeitvorteil in den Selbst-Referenz Durchgängen konnte bei den Patienten nicht beobachtet werden. Der fehlende N400-Effekt in der Patientengruppe kann möglicherweise durch Defizite der Integration und Inhibition erklärt werden. Der Schweregrad der Ich-Störung war desweiteren mit der Stärke des N400-Effekts korreliert. Es wurde daher spekuliert, dass die N400 in der Patientengruppe nicht auslösbar ist, da ein „innerer Prime-Stimulus" aufgrund eines instabilen Selbst-Konzepts fehlt.

In der **Studie II**, mit dem Titel „Neurocognitive profiles in help-seeking individuals: Comparison of risk for psychosis and bipolar disorder criteria " wurden etablierte neurokognitive Tests verwendet um das kognitive Profil von hilfesuchenden Jugendlichen und jungen Erwachsenen zu untersuchen, welche unterschwellige psychotische Symptome zeigten sowie Studienteilnehmer an der prospektiven longitudinalen und multidimensionalen Früherkennungsstudie ZInEP (Zürcher Impulsprogramm zur nachhaltigen Entwicklung der Psychiatrie) waren. Das Ziel war einerseits zu untersuchen, ob die neurokognitiven Messwerte sensitiv genug sind um zwischen einem frühen (High-Risk, HR) und einem späten (Ultra-High-Risk, UHR) Risikozustand zu unterscheiden. Andererseits, ob damit eine Abgrenzung zu Personen mit einem erhöhten Risiko eine Bipolare Störung (HRBip) zu entwickeln, möglich ist. Die Resultate ergaben, dass in Übereinstimmung mit früherer Literatur, die drei Risikogruppen relativ zu der Kontrollgruppe in allen Domänen beeinträchtigt waren. HR und HRBip erzielten vergleichbare Resultate auf einem Niveau welches zwischen der Kontrollgruppe und demjenigen von UHR Probanden lag. Innerhalb der Gruppe der Psychose-Risikoprobanden (HR und UHR) prädizierte die Leistung im Bereich Verarbeitungsgeschwindigkeit eine Gruppenzugehörigkeit zu der UHR Gruppe, während Lern- und Gedächtnisdefizite eine Zugehörigkeit zu der Gruppe vorhersagte, die bis zwei Jahre nach Untersuchungszeitpunkt tatsächlich eine Psychose entwickelten. Die Ergebnisse sind in Einklang mit früheren Studien, welche mögliche Defizite der Verarbeitungsgeschwindigkeit als einen zentralen Risikofaktor postulierten. Die beobachteten schlechten Resultate im Bereich Lernen und Gedächtnis bei den Probanden, die später eine Psychose entwickelten, könnten bereits frühe funktionale degenerative Prozesse wiederspiegeln. Entgegen unserer Hypothese wurden keine Merkmale gefunden, die klar zwischen HR und HRBip Probanden unterschieden. Wir vermuten, dass in diesen frühen Krankheitsstadien mögliche, psychoseassoziierte Einbussen sehr subtil sind und dadurch in unserer Stichprobe durch andere, mit dem Risikostatus assoziierte Merkmale überlagert wurde. Im Allgemeinen hatten die neurokognitiven Defizite einen starken Effekt auf das globale Funktionsniveau und auf die allgemeine Lebenszufriedenheit.

Die Erforschung von Symptomen im Prodrom oder im frühen Psychoserisikozustand scheint vielversprechend, da die konfundierenden Auswirkungen von andauernder Krankheit, Behandlung und anderen Komplikationen vermieden werden kann. Dadurch kann ein besseres Verständnis der pathophysiologischen Veränderungen, welche im Zusammenhang mit der Entstehung von Psychosen auftreten, erreicht werden.

1 Introduction

In schizophrenia, a variety of aspects of behavior, perception, thinking, and emotion are affected. It is among the disorders with the highest burden for those affected (Rössler et al., 2005). A substantial fraction of patients with schizophrenia show a chronic course leading to a high degree of disability (van Os et al., 2009). Hence, schizophrenia is one of the diseases with the highest economic impact worldwide (WHO 2004; van Os et al., 2009). The major peak of first-episode onset occurs typically around late adolescence and early adulthood (Kirkbride et al., 2006). The global lifetime prevalence is estimated of about 0.3–0.7% (van Os et al., 2009), while schizophrenia is thought to affect gender with equal frequency but actually seems to express itself differently (Canuso and Pandino, 2007). Male tend overall to an earlier onset, which has been related to the effect of estrogen to the dopaminergic transmission (Hafner, 1998). The course and outcome of patients diagnosed as having schizophrenia varies extremely with fully remission at the one end and very severe course with progredient deterioration at the other (Menezes et al., 2006). Importantly, five to six years prior to the initial onset of the psychotic syndrome, non-specific signs of illness (prodromal symptoms) have been shown to emerge (Schultze-Lutter et al., 2010). These symptoms are agonizing for those concerned and, in this important early stage of life, can lead to a decline in social functioning and in achievement of educational and occupational matters (Nelson and Yung, 2008; Lin et al., 2011). Therefore a substantial amount of disability is already acquired prior to manifestation of the illness. Additionally, many studies found a longer duration of the untreated psychosis to be linked to more negative outcomes (Marshall et al., 2005). Above all, recent studies have shown that alterations in brain structure (and presumably function) may occur at some point in the transition to full-blown psychosis (Pantelis et al., 2003). Early intervention and prevention strategies with specialized treatment services may effectively influence and enhance the course and prognosis of the illness (Riecher-Rössler et al., 2006; McGorry et al., 2009; Fusar-Poli et al., 2013; van der Gaag, 2013). Ideally, if it might be recognized that an individual is presumably suffering from a prodrome, adequate treatment may be provided at this stage and imminent disability prevented. Monitoring and follow-up assessments may help to detect a conversion to psychosis in a timely manner, and therefore minimize and prevent neurobiological changes and, consequently, a poor rehabilitation associated with it (Yung and Nelson, 2013). Besides the direct relevance for those concerned, a faster remission of symptoms and the prevention or shortening of hospitalization would also contribute to a reduction of costs, especially where social and professional rehabilitation are concerned (Addington and Heinssen, 2012; Mihalopoulos et al., 2009; Riecher-Rössler et al., 2013). To date, even if the available therapies are better than decades ago, an early detection and prevention is considered a very essential strategy to avoid the devastating consequences of the illness.

Schizophrenic psychoses are thought to have a multifactor complex etiology and the pathophysiology is not fully understood (for a review consider Insel et al., 2010). Longitudinal, population-based studies like the Copenhagen or Dunedin birth cohort projects indicated that problems like delayed maturation, including delayed developmental milestones or reduced IQ are in many cases evident before an individual is diagnosed with schizophrenia (Sorensen et al., 2010; Reichenberg et al., 2010). The neurodevelopmental approach (Feinberg, 1982; Weinberger, 1987; Murray et al., 1991) explains the disease originating from disturbed brain maturation processes in prenatal stages (proliferation, migration) and in adolescence and early adulthood (arborization, i.e. circuit formation and myelination) (Insel et al., 2010). The related two hit-model (Bayer et al., 1999) assumes that the transition from a risk through genetic disposition and additional pre- and perinatal risk factors (first hit) into a prodrome and conversion to psychosis is triggered by additional relevant environmental facts (second hit) like social stressors or substance abuse (Falkai et al., 2013). The identification and analysis of enodphenotypes, that is, a quantifiable biological variation or deficit, and thus an indicator of presumed inherited vulnerability to the disease, may help to better understand the disease and ideally, may help to detect individuals with psychotic vulnerability earlier in the course of the illness. There is a substantial amount of literature on disease-related endophenotypes in schizophrenia patients and their first degree relatives comprising structural and functional brain abnormalities, sensory processing and event-related potential measures (i.e. prepuls inhibition, P50, P300, N400), neuromotor abnormalities, neurocognitive measures or impairments in olfactory identification (for a review consider Allen et al., 2009). It is assumed, that the abnormalities appear already early in life and vary qualitatively and quantitatively with brain development and disease progression (Cannon et al., 2003; Falkai et al., 2013; Bora and Murray, 2013).

The present work focuses on the one hand on neurocognitive impairments that are regarded as core symptoms of schizophrenia since its beginning (Bleuler, 1950) and therefore regarded as potential fruitful marker of risk (Seidman et al., 2010; Fusar-Poli et al., 2012a; Riecher-Rössler et al., 2013). On the other hand there is a long tradition of mostly theoretical considerations of a basic self-disturbance being a core feature of schizophrenia (Sass and Parnass, 2003; Parnass and Handest; 2003). Several theoretical and empirical works suggested that phenomenological and neural anomalies reflecting a basic self-disturbance may be a marker of psychotic vulnerability (Nelson et al., 2008). Identifying subtle and self-experienced alterations in cognition and thoughts may inherit potential of detecting individuals at an earlier point in the prodrome and secondly reducing inclusion of "false-positive" by including subjects truly at-risk of psychosis (Nelson et al., 2009).

In the following sections, the theoretical background of the two enclosed studies is introduced (section 1 to 3). Next, the aim of each study is stated in section 4, followed by a description of the methods

used in section 5. The two studies are listed in the section 6 “Empirical work”. Finally, in section 7 the main results of the two studies are discussed and general conclusions were drawn.

1.1 Schizophrenia – definitions

The diagnosis of schizophrenia is based on observed behavior and the patient's reported subjectively experiences, while it should be noted that psychosis is not only occurring in schizophrenia, but other diagnostic categories such as affective psychoses, substance-induced psychotic disorder or psychosis due to a general medical condition (van Os et al, 2009). Frequent symptoms include auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking. To correctly classify schizophrenic psychoses, various aspects like duration, associated dysfunction or substance use, bizarreness of delusions and presence or absence of affective symptoms are considered in the differential diagnostic decisions. The 4th Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and the 10th International Classification of Diseases (ICD-10) offer two ways to satisfy the symptom requirement for schizophrenia: either having one symptom from a list of especially characteristic symptoms (i.e. Schneiderian first-rank symptoms also called ego-pathology or passivity symptoms) or alternatively having two from a list of other psychotic symptoms. Both systems require these symptoms to be present for most of the time for at least one month (van Os et al, 2009). It is debated whether the standard diagnostic criteria for schizophrenia are appropriate for neurobiological studies (First, 2008). Based on the purpose to trying to detect an underlying genetic diathesis to psychosis, a broad definition that would lump together disorders that have been shown to be part of the so called schizophrenia spectrum disorder would be most suited. However, DSM-IV and ICD-10 conceptualize schizophrenia as a categorical diagnosis, that is, according to these systems an individual either has or does not have schizophrenia. Cloninger (1999) stated about this that the assumption that psychiatric disorders are discrete entities that can be categorically defined is “inconsistent with available knowledge of the psychobiology, genetics, development and evolution of thoughts, emotions and behavior “(p.174). It is already accepted that delusions and hallucinations have a continuous distribution in the general population (Kendler et al., 1996; Rössler et al., 2007). Furthermore, treatment studies and genetic studies suggest that schizophrenia and bipolar disorder may share important underlying elements (Casey et al., 2003; Cardno et al., 2002).

However the analysis of the psychopathological features in the various psychotic disorders suggests that symptoms can be clustered into five main categories: (i) psychosis (encompassing delusions and hallucinations—also called the positive-symptom dimension); (ii) alterations in drive and volition (lack of motivation, reduction in spontaneous speech, and social withdrawal—the negative-symptom dimension); (iii) alterations in neurocognition (difficulties in memory, attention, and executive functioning—the cognitive-symptom dimension); and (iv and v) affective dysregulation giving rise to

depressive and manic (bipolar) symptoms (van Os et al., 2009). In the enclosed study I we focus on schizophrenia patients suffering mainly one type of positive symptoms, that is, ego-pathology.

1.2 The psychosis High-Risk state

In medicine, the term prodrome depicts a state with early unspecific symptoms that might indicate the start of a disease before characteristic symptoms occur (Mifflin, 2007). The diagnosis of a prodrome can only correctly be made retrospectively after manifestation of the illness. To avoid such inconsistency an alternative labeling of subjects potentially suffering from a prodrome has been introduced to research related to early detection of psychosis (Schultze-Lutter et al., 2011). The most frequently used terms are at-risk mental state (ARMS), ultra-high risk (mental) state (UHR) or clinical high risk state (CHR) (Schultze-Lutter et al., 2011). The symptoms occurring in the prodrome are rather non-specific, and develop in a subtle manner, and are therefore often misinterpreted as a reaction to the strains of everyday life than possible early symptoms of a psychosis. Symptoms that may arise include anxiety and affective symptoms, nervousness, difficulties in sleep, concentrating, or feelings of social insecurity as well as more characteristic ones like increased mistrust, feelings of unreality, confused thoughts or unusual perceptions. With the help of checklists, an initial tentative statement can be made about whether an increased risk of psychosis exists and further assessments may be advisable (e.g. Häfner et al., 2011).

UHR **Ultra High-Risk criterion** **Late at-risk of psychosis state**
Attenuated positive symptoms APS
Ideas of reference
Unusual thought content / magical thinking
Perceptual abnormalities
Odd thinking and speech
Paranoid ideation
Brief limited intermittent psychotic symptoms BLIPS
Hallucinations
Delusions
Formal thought disorder
State-Trait Criterion
Risk (family history of psychosis or schizotypal personality)
Unspecific symptoms (e.g. anxiety, depression)
Reduction in global assessment of functioning of >30% in the past year).

Tab. 1 Ultra-High-Risk criteria of schizophrenia.

Today, for the clinical characterization of the psychosis high-risk state clear guidelines exist (Fusar-Poli et al., 2013). The combination of many different symptoms, but also the intensity of a single symptom, can signify that a person is at a particular risk of developing a psychosis. As such is suggested to diagnose the (late) "prodromal phase" of schizophrenic psychosis with the manifestation of attenuated positive symptoms (APS) or brief intermittent psychotic symptoms (BLIPS) implemented in the ultra-high-risk (UHR) criterion of Yung and MCGorry (1996). APS describe subthreshold positive symptoms held with either subthreshold frequency

or subthreshold intensity present for at least one week. BLIPS on the other hand are transient psychotic symptoms, that is, psychotic symptoms present for less than one week with spontaneous remission. Additionally, a state-trait criterion (or genetic risk and deterioration syndrome) is used for diagnosis (see Table 1).

Different psychopathological interviews have been developed to assess UHR features and to determine whether individuals meet the previously mentioned criteria (for an overview consider Schultze-Lutter and Ruhrmann, 2008). Time and onset/worsening criteria slightly vary between the instruments.

A putatively even earlier prodromal state, the high-risk (HR) criterion, was described by Huber (1966), in which help-seeking individuals mainly describe the disturbing experience of so called "basic symptoms", which are subtle and self-reported alterations and deficits observed in cognition, thoughts and perception (Klosterkotter et al., 2001) (see Table 2). Basic symptoms are distinct from classic psychotic symptoms for that it is assumed that individuals with this condition crucially still have 'insight', indicating that the altered worldview can be reflected and the reference to reality still is intact (Schultze-Lutter, 2009). More recently, basic symptoms are increasingly assessed over the Schizophrenia Proneness Instrument, adult version (SPI-A) and child and youth version (SPI-CY) (Schultze-Lutter et al., 2007; Schultze-Lutter and Koch, 2009).

HR **High-Risk criterion** **Early at-risk of psychosis state**
Basic symptoms BS
COPER: cognitive-perceptive symptoms
Thought perseveration
Decreased ability to discriminate between ideas and true memories
Derealisation
Visual perception disturbances
Acoustic perception disturbances
COGDIS: cognitive disturbance
Inability to divide attention
Disturbance of expressive speech
Disturbance of abstract thinking
Captivation of attention by details
COPER and COGDIS
Thought interference
Thought pressure
Disturbance of receptive speech
Unstable ideas of reference

Tab. 2 High-Risk criteria of schizophrenia.

On the basis of different prospective studies, a progression of symptom development relating to the symptomatic definition of early and late at-risk state was proposed (Klosterkotter et al., 2003). The illness typically begins with unspecific problems, followed by predictive basic symptoms and, subsequently by APS, before transient BLIPS and psychotic symptoms develop (Schultze-Lutter et al., 2010) (see Figure 1).

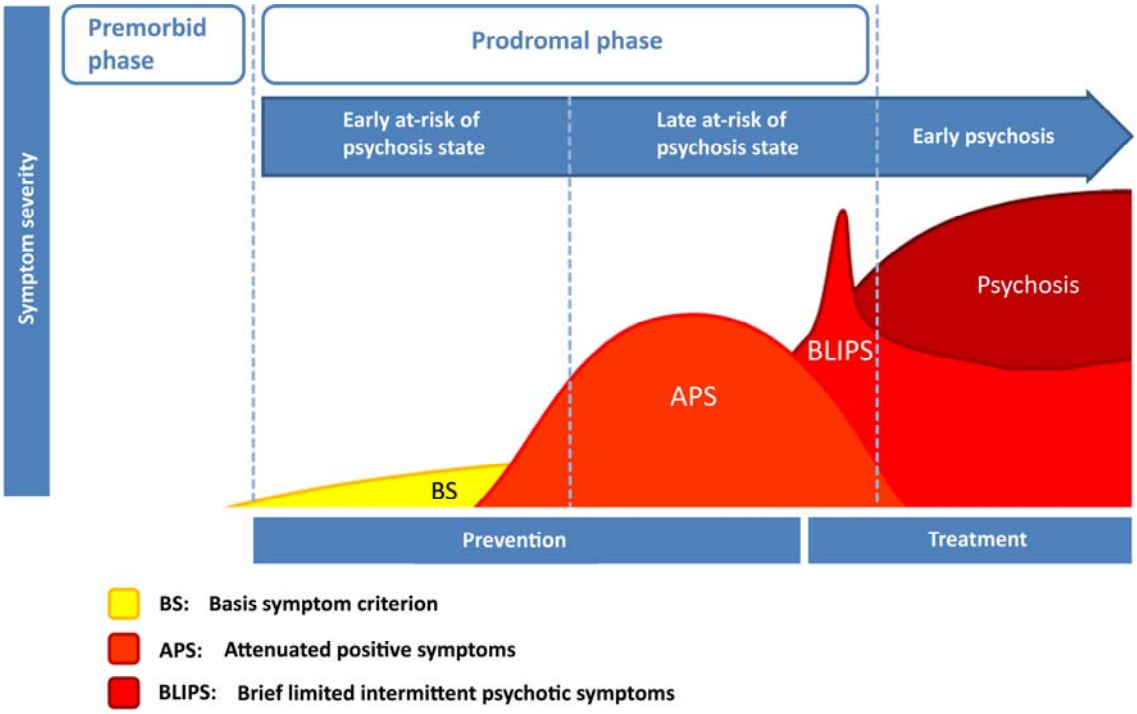

Fig. 1 Progression of symptoms from premorbid phase to psychosis onset (according to Fusar-Poli et al., 2013).

A recent meta-analysis revealed that the transition risk to psychosis in at-risk samples is mean (95% CI) and independently of psychometric instruments used, of 18% at 6 months, 22% at one year , 29% at two years and 36% at three years of follow-up (Fusar-Poli et al., 2012b). However, these facts indicate also, that in a substantial fraction of the at-risk psychosis labeled subjects a conversion to psychosis may not be observed. This is a debated issue, especially because a potential unnecessary diagnosis might give rise to unintended consequences like stigma and discrimination (Yung et al., 2010). To address open questions regarding those possible disadvantages associated with the at-risk state, any perceived stigma, and comparison made with the stigma and stereotypes were assessed in the ZInEP study. We could already show that especially self-labeling and perceived public stigma appeared to be associated with heightened stress through stigma associated cognitions and delicately reduced well-being of the young individuals (Ruesch et al., submitted). Therefore it seems that more research related to the possible side-effects of the labelling as at-risk of psychosis is urgently needed (Yung et al., 2012; Ruesch et al., submitted).

2 Ego-pathology in schizophrenia

In the early 20th century, the psychiatrist Kurt Schneider listed the forms of psychotic symptoms that he thought distinguished schizophrenia from other psychotic disorders (1959). These so called first-rank symptoms or Schneider's first-rank symptoms are thought to inherit a high diagnostic value (Leube and Pauly, 2008). Symptoms include delusions of being controlled by an external force, the belief that thoughts are being inserted into or withdrawn from one's conscious mind, the belief that one's thoughts are being broadcast to other people, and hearing hallucinatory voices that comment on one's thoughts or actions or that have a conversation with other hallucinated voices. In the German speaking area ego-pathology symptoms are rated with the handbook of AMDP (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie, *Ich-Störungen*). The symptoms of derealisation or depersonalisation are not directly accounted to first-rank symptoms as they are not accompanied by the connotation of passivity ("Gefühl des Gemachten") that is, a loss of feeling of agency (see below). Furthermore they are less specific for schizophrenia as they have shown to be frequent in attenuated forms in healthy individuals under extreme fatigue as well as in depression (Leube and Pauly, 2008). In international research the Standard Assessment of Positive Symptoms (SAPS; Andreasen, 1984) is used to assess these symptoms, although a score for ego-pathology is missing in the system. This fact may reflect the Anglo-Saxon tradition to treat ego-pathologies not as a separate symptom but to account them to delusions, outlined as "passivity symptoms", that is, delusions of influence or delusions of control (Leube and Pauly, 2008). In the study I of this work, ego-pathology was rated on the SAPS and grouped together to an ego-pathology score implemented before by Pauly et al. (2011).

2.1 Self-disturbance in the at-risk psychosis state

Qualitative studies suggest that signs of a disturbed perception of the self may be observed already in the prodrome and might include various symptoms such as: diminished sense of basic self (such as sense of inner void, lack of identity, being different from others), sense of distance between the self and experience (spatialisation of the self, varieties of depersonalization), decreased ability to be affected by objects, people, events (e.g. diminished feeling of presence), loss of "common sense" and perplexity, that is difficulties to automatically grasp the meaning of everyday's events (Nelson et al., 2009). The self-disturbance seen in prodromals is not of psychotic intensity (as it is in ego-pathology symptoms) because subjects still have insight. Typically the individuals connote to the symptoms they are suffering from a subjective feeling of "as if" (e.g. "it felt *as if* the thoughts were not mine) (Nelson et al., 2009). Help-seeking young adults may be questioned about the subtle and self-reported alterations in thoughts perceptions within a semi-structured interview such as SPI-A or SPI-CY. In the transition to frank psychosis these anomalies are strengthen and emerge in form of delusions,

hallucinations and passivity phenomena. The various types of self-disturbance may also rated on the elaborate Examination of Anomalous Self Experience inventory (EASE; Parnas, 2006) as suggested by the Copenhagen Prodromal Project. There are indications that the phenomenological disturbances may assist in the identification of "true positives" within at-risk psychosis samples (Hoffman et al., 2007; Nelson et al., 2012).

2.2 Linking phenomenology of self-disturbance and neurobiology

Notions of "the self" vary with discipline involved and aspect of the complex linguistic construct meant as the self is regarded as a multidimensional phenomenon (James, 1890; Neisser, 1988; Gallagher, 2000; Damasio, 2003). Therefore, related work has specified two to three levels of selfhood (pre-reflective, reflective and social self) (Nelson 2009). Foremost, a subjective first-person perspective is thought to be needed to interact with and reflect on objects or other persons. This aspect of consciousness is thought to occur pre-reflectively and is the basis upon which any other type of self-consciousness evolves. It is needed to perceive ourselves as the immediate subject of experience. Each reflection and cognition related to the perception of the self as subject changes the perspective of the self immediately to the one of an object: as soon as the "I" reflects about itself it changes to "me". In other words, we cannot contemplate our "self"as subject but only as an object, that is, in reflective self-reference, since the perspectives of subject and object exclude each other (Legrand, 2007). In line with this theoretical assumption, recent neurobioloical research distinguishes at least two types of self-concept, that is first, a pre-reflective, sensorimotor-based bodily self and second, a higher-level, reflective self referring e.g. to autobiographical memory or self-recognition (e.g. Legrand and Ruby, 2009). Further, the pre-reflective aspect of self is thought to consist of two closely related aspects: the sense of agency and the sense of ownership, e.g. the sense that *I* am thinking my own thoughts or that it is *my* body that is moving. The temporoparietal junction is thought to constitute an important neural substrate that is allowing one's experience as being embodied through multisensory perception and integration (Lenggenhager et al., 2006).

2.3 Self-monitoring and aberrant salience

On the suggested levels of selfhood (pre-reflective, reflective and social self), the phenomenological model of self-disturbance in schizophrenia spectrum disorders suggests that the disorder of self occurs at the level of the pre-reflective self, in contrast to the disordered self in non-schizophrenia spectrum personality disorders, such as borderline or narcisstic personality disorder, where the self is assumed to be disturbed on the level of social self, with a more basic sense of self remaining intact (Parnas and Handest, 2003). Nevertheless, the disturbance on the pre-reflective level may additionally affect and disrupt higher cognitive functioning and affects cohesion in auditory, visual or tactile senses as well

as thought and speech (Nelson et al., 2009). It has been proposed that so called source or self-monitoring deficits (Ditman and Kuperberg, 2005) may particularly explain disturbances of ownership while aberrant salience (Kapur, 2003; Kapur et al., 2005) and associated disturbances of memory and attention processes may contribute to hyper-reflexivity and disturbances of intuitive social understanding (Nelson et al., 2013).

According to the **source or self-monitoring model** the disturbance of self seen in schizophrenia is caused by a difficulty distinguishing between the origins of endogenously and exogenously generated stimuli (Ditman and Kuperberg 2005; Jeannerod, 2009). Positive symptoms such as auditory hallucinations and passivity phenomena are thought to result from misattribution of internal thoughts and actions (inner speech or motor commands) to external sources. Dysfunction of mechanisms efference copies or mirror neurons may be the basis on which the errors in source attribution evolve from (Jeannerod, 2008). A dysfunctional representation or labelling of actions and thoughts in the parietal cortex (Jeannerod et al., 2008) or in frontal areas (Gusnard et al., 2001) at the time of their generation may result in non-attributed or misattributed actions or thoughts and give raise to the symptoms. Thereby the role of the medial prefrontal cortex involves interactions with domain specific processes mediated by other brain areas such as lateral temporal areas for making correct source attributions about verbal stimuli (Allen et al., 2005; Fu et al., 2008) or with inferior parietal and cerebellar regions in the sensorimotor domain (Blakemore et al., 2003). Delusions of control as the loss of the feeling of authorship (sense of agency) or feeling of "mineness" (sense of ownership) on a thought or action has been studied with various paradigms (Tsakiris, 2010). In patients with schizophrenia and in individuals at-risk of psychosis both aspects have been shown to be disturbed or altered (Hauser et al., 2011a; Hauser et al., 2011b; Rains et al., 2012; Thakkar et al., 2011; Wilquin and Delevoye-Turrell, 2012).

Consistent with this view findings from studies applying intrinsic functional connectivity analysis revealed that aberrant functional (effective) connectivity between medial prefrontal and lateral temporal cortex played a critical role in causing misattribution errors (Mechelli et al., 2003; Wotruba et al., accepted). Particular attention has been given to disturbances of the default mode network (DMN), which is thought to support introspection and mental simulation or episodic retrieval (Gusnard et al., 2001; Fox and Greicius et al., 2005; Raichle and Snyder, 2007) and the task positive network (TPN), which supports externally focused attention (Williamson et al., 2007; Woodward et al., 2011; Chai et al., 2011). The DMN has been shown to be negatively correlated with activity in the dorsolateral prefrontal cortex and posterior parietal cortex that form the TPN (also referred to as central- executive network), a set of regions that are activated during goal-oriented activity (Fox et al., 2005; Wotruba et al., accepted). The findings of abnormalities in the coordination of DMN and TPN in schizophrenia have also been related to impairments in attention and working memory as well as

increased self-referential and introspective processing (Whitfield-Gabrieli and Ford, 2012; Van Buuren et al., 2012; Wotruba et al., accepted).

The functional competition between the internally directed DMN and externally focused TPN is thought to be regulated by the **salience network (SN)** (Seeley et al., 2007; Sridharan et al., 2008). The term salience is used to describe the relative amount of attention directed towards a stimulus compared to other stimuli (i.e. how prominent or important a stimulus appears to be) and the resulting effect on goal-directed behavior (Kapur, 2003; Kapur et al., 2005). Deficits in the suppression of attention directed towards irrelevant or familiar stimuli, or in other words, excessive attention to information that is irrelevant or already highly familiar, leads to aberrant salience of objects and associations. In schizophrenia aberrant salience has been linked to failure of suppression of irrelevant stimuli on behavioural or cognitive level (Morris et al., 2012) or weakening of contextual constraint (e.g. *theory of mind* (Uhlhaas et al., 2006); *N400* (Kiang et al., 2008); for review see Nelson et al., 2013). Keefe and colleagues (2009) have recently introduced a "memory prediction" model of cortical function which helps to explain the slowed and more effortful processing of incoming information and the increase of randomly, internally oriented interpretation of stimuli. According to this model, common and usually automatic processed stimuli become unfamiliar due to failings in "top-down" processes (ability to "fill the gaps") and flagged for more deliberate analysis by higher cortical areas. Likewise it may be assumed that in schizophrenia the reduced N400 following unexpected stimuli may be an expression of this. According to pharmacological models, aberrant dopamine transmission may increase the salience of internal and external stimuli making it difficult for patients to adaptively focus and shift their attention (Corlett et al., 2007; Kapur, 2003; Kapur et al., 2005). Positive symptoms may thus arise as patients experience and try to make sense of these abnormal salient stimuli (Nelson et al., 2013)

Many studies so far have investigated self-referential processing in healthy individuals using a study paradigm in which subjects had to reflect on their own personality traits using functional neuroimaging methods (for a review consider Northoff et al, 2006) or electrical tomographic techniques (Esslen et al., 2008). According to this field of research, in healthy subjects, cortical midline structures are considered being essentially involved in self-referential processing and internally directed attention (Gusnard et al., 2001; Northoff, 2006). A direct comparison of default and self-reference networks further revealed that explicit self-reference engaged dorsal MPFC, while default conditions preferentially engaged precuneus and both engaged ventral MFPC and precuneus. This may suggest that the activity during default condition in ventral MPFC and PCC may be a product of self-referential thought in absence of attention to external stimuli (Whitfield-Gabrieli et al.,

2011). Symptoms of hyper-reflexivity and diminished self-affection seen in prodromals would thus suggest an increase of activity in cortical midline structures (Nelson et al., 2013).

[„Ich bin ein Korb, dessen Inhalt zerstreut am Boden herumliegt
und ich kann ihn nicht mehr sammeln und ordnen.“]
(Schizophrenia patient, quoted according to Bleuler 1916)

3 Neurocognitive deficits in schizophrenia

Cognitive dysfunctions in schizophrenia and their neurophysiological and anatomical correlates have been extensively studied. Many researchers speak of it as a robust feature of schizophrenia, that is, as a central manifestation of the pathophysiology of the disorder (Bleuler, 1950; Schultze-Rauschenbach, 2007; van Os and Kapur, 2009). Today it is accepted that schizophrenia patients exhibit global neuropsychological deficits of, on average, about one to two standard deviations below the mean performed by healthy individuals (Fioravanti et al., 2005). Accentuations in specific functions are assumed most consistently in attention, speed of processing, working memory, long-term memory, executive function and social cognition (van Os and Kapur, 2009; Fusar-Poli et al., 2012a). Up to now the association between cognitive impairments and severity of positive and negative symptoms in schizophrenia is unclear. They might be not or only moderately correlated (Dominquez et al., 2009). The findings regarding progression of these cognitive deficits over the course of the disorder is conversely discussed not least due to a substantial amount of confounding variables associated with chronicity such as antipsychotic medication, institutionalization or poor physical health (Fusar-Poli et al., 2012a). Concerning verbal memory some evidence of further deterioration after initial onset of the illness has been found, while deficits in other functions have been observed to remain stable over a certain time (Brewer et al., 2006). It is assumed that the deficits seen in schizophrenia are not solely a consequence of disease related neurodegenerative processes, but manifest to a great extent already early as neurodevelopmental abnormalities prior to first episode of the illness (Fusar-Poli et al., 2012a). This was again confirmed by a recent study across a large population of young Swiss conscripts reporting significantly more often indicators of cognitive problems in individuals that were later diagnosed with schizophrenia (Müller et al., 2013). The neurocognitive impairments are thought to be measurable before the onset of the illness and it is hoped that they may serve as additional indicator helping to optimize the at risk prediction criteria (Riecher-Rössler et al., 2013).

The neurodevelopmental model assumes a genetic-biological determined vulnerability leading to instability in brain development already pre-birth, likely in terms of deficits in cerebral maturations (Insel et al., 2010). The disordered processes may affect brain maturation as well as maintenance of

crucial processes in the mature brain such as reparative processes, i.e. synaptogenesis and neuroneogenesis (Reif et al., 2006). Reductions in hippocampal volume are therefore most likely explained by disordered reparative processes which impress as functional degeneration. Furthermore, family studies showed that certain brain structural (e.g. hippocampal) changes as well as cognitive deficits also to be likely in first-grade relatives of affected individuals without leading to psychopathological abnormalities (for review see Falkai et al., 2013). This fact may suggest that a genetic predisposition might contribute to both, later performance in neurocognition and increased risk of psychosis (Müller et al., 2013).

3.1 Neurocognitive deficits as predictors of psychotic vulnerability

Across studies, severity of attenuated positive symptoms, poor social functioning, substance abuse, and genetic risk for schizophrenia appeared to be consistent predictors of conversion to psychosis (for a reviews see Gee and Cannon 2010; De Herdt et al., 2013). Nevertheless, additional predictive biomarkers such as performance in certain neurocognitive measures may increase the reliability of identifying individuals in a potential at risk state for developing psychosis. Multilevel assessment approaches as used in the Zurich Program for sustainable Development of Mental Health Services (ZInEP) early detection project or described by Riecher-Rössler et al. (2013) include neurocognition as one domain among others like specific interview for anamnesis, various scale for psychopathology, EEG, MRI of the brain, and laboratory to study the appearance of symptoms in the at-risk states psychosis state. It has already been shown, that a specific tool for anamnesis and psychopathology like the BSIP used by the FEPSY ("Früherkennung von Psychosen") group provided a relatively reliable prediction of 39.6% of individuals identified as at risk which converted to psychosis within the follow-up time. Nevertheless, the prediction could be improved up to 81% by weighting psychopathology and including measures of neurocognition (Riecher-Rössler et al., 2013).

Studies on at risk psychosis individuals matched with healthy controls found small to medium impairments across most neurocognitive domains in at-risk psychosis subjects that were at intermediate level between that of healthy individuals and those diagnosed with schizophrenia (Hawkins et al., 2004; Brewer et al., 2006; Pukrop et al., 2006; Eastvold et al., 2007; Fusar-Poli et al., 2012a). Moreover, at-risk subjects who later converted to psychosis showed more severe neurocognitive deficits at baseline than nonconverter in almost all domains (Seidman et al., 2010), but especially in the domains of speed, verbal fluency and memory (Giuliano et al., 2012, Pukrop and Klosterkötter, 2010). A number of "specific" deficits, presumably above and beyond any "general" deficit, have been documented in at risk psychosis samples, such as verbal learning and memory (Brewer et al., 2005; Eastvold et al., 2007; Hawkins et al., 2004; Lencz et al., 2006; Seidman et al.,

2010), attention (Gschwandtner et al., 2006; Hambrecht et al., 2002; Hawkins et al., 2004; Niendam et al., 2006) and processing speed (Seidman et al., 2010). Executive functions such as working memory, verbal fluency, and set-shifting have also been implicated, but less consistently (Eastvold et al., 2007; Gschwandtner et al., 2006; Hambrecht et al., 2002; Hawkins et al., 2004; Lencz et al., 2006; Pukrop et al., 2006; Simon et al., 2007). Verbal memory and processing speed have been repeatedly associated with psychosis conversion (Lencz et al., 2006; Pukrop et al., 2007; Lin et al., 2011; de Herdt et al., 2013). In the study with a stepwise approach of Riecher-Rössler (2013) it has been shown that a poor result in a task testing selective attention and reaction inhibition (TAP) heighted the prediction accuracy in a logistic regression model together with psychotic (suspiciousness) and negative symptoms (anhedonia/asociality) rated on the SANS.

In an earlier prospective birth cohort study found that subjects who later developed a schizophrenic disorder compared to those who subsequently developed an affective disorder showed at baseline assessment already marked impairments in tasks that involve psychomotor speed as well as attentional and executive abilities (a combined score of Trail-making Test and Digit Symbol Coding Test) (Cannon et al., 2006). In line with this, a recent community based study found in at-risk psychosis subjects the deficits in speed domain to be most pronounced (Kelleher et al., 2013). However the ability to draw conclusions about specific deficits underlying psychotic vulnerability is limited because of several methodological issues. Foremost, conceptual heterogeneity in the labeling and construction of cognitive domains leads to inconsistent findings (Pukrop and Klosterkotter, 2010). For example, Cannon and collegues (2006) and Kelleher and colleques (2012) included Trail-making and Digit Symbol Coding Tests in their functional domain “processing speed” whereas Frommann and collegues (2011) additionally included measures of verbal fluency and labeled the functional domain “executive control/processing speed”. The usage of populations norms for individual tests obtained from different normative samples may diminish the comparability between studies. Further, studies relied on different assumptions relating to general level of intelligence, therefore control subjects were not always comparable regarding premorbid intellectual functioning. Test selection and complexity varies across studies, as well as variables of single tests or composite scores with unconfirmed factor structures were used. Finally, sample sizes often consisted mainly of patients exhibiting APS, only few studies directly compared early and late at-risk state (Frommann et al., 2011). Most of the above-mentioned issues were tried to address in the enclosed study II.

4 Aims

4.1 Aims Study I

Study I, entitled "Evaluation of trait adjectives and ego pathology in schizophrenia: an N400 study." was designed to investigate the network of self-related reflective self in schizophrenia using the N400 related components in an electrophysiological recording. An alteration of the N400 in patients suffering from schizophrenia has been reported in many studies (Adams et al., 1993; Nestor et al., 1997; Ohta et al., 1999; Salisbury, 2010). An abnormal activation and organization of the semantic memory associative networks coupled with a decay of verbal working memory maintenance in schizophrenia is discussed to be accountable for these alterations (Salisbury, 2010). Deficits in mechanisms connected upstream of speech production may be accountable for the observed idiosyncratic speech seen mainly in formal thought disorder symptoms (Mohammad, 2013) where a looseness of associations and loss of purpose in the chain of thought impress as deficits in executive function and self-monitoring. We speculated that in patients suffering prominent ego-pathology symptoms similar mechanisms might have lead to alterations in the associative self-reflective memory which in turn leads to an experienced loss of individuality and sense of autonomy. Higher cognitive processes such as over attribution or the avoidance of cognitive dissonance may subsequently lead to a changed concept of self as well as meta-cognition of others. To study the network and organization of self-related reflective memory in patients exhibiting ego-pathology, a study paradigm was implemented that has been used before to engage subjects in self-referential mental activity (Esslen et al., 2008). Specifically, subjects viewed trait adjectives and indicated whether or not they applied to themselves, or to another predefined person. Since the N400 is not only elicited by sentence endings that belong to related semantic categories, but also by those that are unexpected (Kutas and Hillyard, 1984), we hypothesized that in controls a stronger N400 should be generated with adjectives that are rated as incongruent or unexpected by the study participants compared to congruent adjectives. For the schizophrenia patients we hypothesized that they would exhibit a smaller than normal N400 effect (i.e. that the difference in the activation after an incongruent word is similar to the activation to a congruent word) in line with the view that the primary memory functional organization deficit in schizophrenia facilitates the integration of the unexpected and incongruent word. The aims were further to explore on the one hand if the severity of the underlying ego-pathology were associated with altered N400 components and on the other hand, if behaviorally, patients and controls respond differently to the stimuli.

4.2 Aims of Study II

This study II, entitled "Neurocognitive profiles in help-seeking individuals: Comparison of risk for psychosis and bipolar disorder criteria" aims to explore the neurocognitive functioning in different at-risk population and to investigate whether neurocognitive measures are sensitive enough to differentiate an early and late at-risk psychosis state as well as an at-risk bipolar state. The study extends previous research by addressing the neurocognitive functions and clinical characteristics not only of persons at high and ultra-high risk of schizophrenic psychosis but also of subjects at-risk for bipolar disorder, in comparison to a group of matched healthy controls. Neurocognitive measures of help-seeking individuals which could be identified as high-risk (HR) and ultra-high risk (UHR) of schizophrenic psychosis as well as high-risk of bipolar disorder were grouped according their load in factor analysis and compared among the groups as well as the probabilities for a given group were estimated using logistic regression analyses. We hypothesize mainly that (i) HR and UHR exhibit generalized neurocognitive deficits compared to the control group, (ii) that deficits in measures of learning and memory are associated with more severe psychopathological symptoms, and (iii) that the HRbip group exhibits less or no deficits on psychomotor speed dependant tasks than the UHR and HR group.

5 Methods

The next sections refer to the methods used in the two presented studies to investigate the cognitive processes in the brain, namely Electroencephalography (EEG) and a battery of neurocognitive tests. The EEG measures the neuronal electrical activity derived on the surface of the scalp and provides an excellent time resolution in the range of milliseconds. Compaired to other methods used in the field of neuroscience it represents a favorable tool providing insight into the temporal dynamics of brain processes (Michel et al., 2009). Despite advances in brain imaging technology, it is already well known, that the presence of significant brain changes may be associated with nearly normal cognitive functioning, while individuals with normal findings in clinical brain imaging may have substantial cognitive and functional limitations (Harvey, 2012). The neuropsycholocigal assessment is thus still seen as a useful tool to add critical information to psychological, neurological, or neuroimaging assessments. The following section gives a brief introduction into these methods.

5.1 Electroencephalography

Electroencephalography (EEG) is a non-invasive technique used to record the oscillation of brain electric potentials along the scalp, i.e. voltage fluctuations resulting from ionic current flows within the neurons of the brain (Jäncke, 2005). The EEG represents the oldest technique that directly measures the electrical activity of the brain. It was invented and described by Hans Berger (1929), who already noticed that the EEG appears to be a sensitive indicator of mental states. Eighty years later, recording and analysis methods exist that have made EEG a widespread and validated tool to observe the spatial and temporal dynamics of brain network activity during a large variety of mental states and processes in a completely noninvasive fashion (Michel et al., 2009). The EEG technique may be used to investigate the neurophysiological correlates of cognitive or stimulus-driven brain functions as well as to determine the resting-state modus of the brain. Despite limited spatial resolution, EEG continues to be a valuable tool for research and diagnosis, especially when millisecond-range temporal resolution is required (Michel et al., 2009).

For measuring the EEG signal, electrodes are placed on the surface of the scalp with standardized configurations (Jasper, 1958). Electrical activity arising from thousands of synchronously activated neurons is recorded. The active cortical neurons produce currents spreading passively through the brain, cerebrospinal fluids, skull and the scalp. Finally, these currents reach the scalp surface, upon which the voltage differences between each electrode and the reference electrode are computed.
The EEG oscillations are mainly generated by postsynaptic potentials of pyramidal cells in the cortex (Birbaumer and Schmidt, 2003). Neural activity is produced by releasing neurotransmitters in the

synaptic gap, whereas signals are transmitted from one neuron to the target neuron. The synaptic activity can either produce excitatory (EPSP) or inhibitory (IPSP) postsynaptic potentials across the membrane of the target neuron. Hence, neural activity is accompanied by a negative or positive shift of the resting state. IPSP produces inhibitory effects on the target neuron while EPSPs facilitate the generation of an action potential (depolarization). The EPSP allows the inflow of positive ions from the extracellular to the negative charged intracellular space. This shift in postsynaptic potentials induces an electrical dipole which is derived on the cortical surface when several thousand cortical neurons are active synchronously. In order to be measured by EEG electrodes, the induced current has to flow through brain tissue and liquor, well as through the skull and scalp. Since the current of a single nerve cell is very small, thousands of synchronously activated neurons are required for generating a measurable electrical signal at the surface of the scalp. Consequently, the EEG is only sensitive to a large number of simultaneously activated nerve cells (Birbaumer and Schmidt, 2003).

Event-Related Potentials

Event-related potentials (ERPs) refer to averaged EEG responses that are time-locked to a specific visual, auditory or cognitive event (Jäncke et al., 2005). The EEG reflects thousands of simultaneously ongoing brain processes. Therefore, the brain response to a single stimulus or event of interest is usually not visible in the EEG recording of a single trial because the random (background) brain activity together with other bio-signals and electromagnetic interference constitute the noise contribution to the recorded ERP. Summing up and averaging of multiple recorded time segments enhances the signal-to-noise ratio (SNR) by causing random brain activity to decrease and enabling the ERPs become discernible for interpretation (Coles et al., 1996). The present work focuses on a particular event-related response, namely on the N400 component. This ERP component has repeatedly been shown to be sensitive to lexical and semantic processing, and to have maximal magnitude at centro-parietal scalp sides.

3.2 Neurocognitive assessment

The neurocognitive assessment is a performance-based method to assess cognition, which subsumes all mental processes and functions responsible for the human brain to perceive and act to its environment including for instance memory, perception, attention, language, problem solving or planning as well as motivation (Karnath, 2006). This method is clinically used as neuropsychological assessment to examine the cognitive consequences of brain damage or severe mental illness in which the collection of additional diagnostic and differential diagnostic information, as well as assessment of treatment response, cognitive remediation and prediction of functional potential and recovery are specifically of importance (Harvey, 2012).

The standardized and validated neurocognitive tests have been designed to link the test performance to specific neurocognitive processes. In the study II a set of well-established neuropsychological tests shown to be sensitive to discriminate between clinical high risk and healthy controls were administered in a fixed order. Verbal premorbid IQ was estimated with a word recognition test (MWT-B; Lehrl, 1999) for adults and a test of receptive vocabulary for minors (PPVT; Dunn and Dunn 1981). Measures of attention were assessed by the Continuous Performance Test (CPT-OX; Beck et al., 1956). The Trail Making Test parts A and B (Reitan, 1992) as well as subtests of the Wechsler Adult Intelligence Scale (WIE) (Aster et al., 2006) were used to assess psychomotor speed, attention and cognitive flexibility. Measures of verbal and figural learning and memory were collected from a German auditory verbal learning test (Helmstaedter et al., 2001) and from the Rey Visual Design Learning Test (Bay, 1964, in: Spreen and Strauss, 1991). Measures of executive function were provided by a test of verbal fluency (RWT; Aschenbrenner et al., 2000), working memory (subtests of the WIE, Aster et al., 2006) and the computer-administered Wisconsin Card Sorting Test (CKV; Drühe-Wienholt and Wienholt 2004) and Tower of Hanoi test (ToH; Gediga and Schöttke, 1994).

6 Empirical part

6.1 Study I: Evaluation of trait adjectives and ego pathology in schizophrenia: an N400 study.

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Abstract

The N400, an event-related brain potential (ERP), can be triggered by semantic or arithmetic violations in visual or auditory stimulus material. Schizophrenia patients exhibit an altered N400 presumably resulting from impaired semantic memory associative networks. The present study investigates, whether an altered N400 can also be found in semantic violations of the own self-concept. We use simple descriptive sentences to combine semantics with the self-concept in order to explore differences and possible deficits in schizophrenia patients.

Schizophrenia patients and controls were shown trait adjectives in reference to themselves. Participants had to decide if the presented trait adjective was congruent or incongruent with their own self-concept. Only in controls, the N400 was significantly more negative in the incongruent compared to the congruent condition. Controls seemed to profit from a stable self-concept as they were faster in judging if a given trait was descriptive for the self than for someone else, which might likely result from processes related to the self-reference effect. Interestingly, in schizophrenia patients, the higher the scores for ego pathology were, the smaller the N400 effect turned out to be. The diminished N400 effect is probably associated with a disturbed self-concept in schizophrenia.

Keywords: psychosis; self-reference, ego pathology, self-concept; ERP (event related potential); N400

1. Introduction

Semantic processes are among the cognitive functions that have been widely studied in schizophrenia (Brebion et al., 2013). The N400, an ERP component at approximately 400ms post-stimulus, is evoked by any potentially meaningful stimulus and is thought to reflect semantic processing of information such as language, numbers or pictures. It is more pronounced after incongruent than congruent sentence endings as well as after weakly associated words compared to strongly associated words (Kutas and Hillyard, 1980; Kutas and Federmeier, 2000; Duncan et al., 2009). Semantic inhibition processes contribute to the N400 effect by increasing its amplitude to incongruent information (Debruille, 2007a). Only a small amount of knowledge, activated by a word, is actually integrated into the current context, additional inhibition processes have to filter out irrelevant representations. Differences in the inhibitory processes may contribute to the variability of the N400 amplitudes. Hence, situations that need more inhibition will result in more negative N400 components.

An alteration of the N400 in patients suffering from schizophrenia has been reported in many studies (Adams et al., 1993; Nestor et al., 1997; Ohta et al., 1999; Salisbury, 2010a). Compared to healthy controls, the difference between N400 amplitudes elicited by congruent and incongruent sentence endings is commonly reduced in schizophrenia patients (Mitchell et al., 1991; Adams et al., 1993; Kiang et al., 2008; Salisbury, 2010a). An abnormal activation of the semantic memory associative networks coupled with a decay of verbal working memory maintenance in schizophrenia is discussed to be accountable for these alterations (Salisbury, 2010a). However, the generation of N400 is not completely disturbed in schizophrenia. Schizophrenic patients are in fact able to generate a N400 dependent on the severity of semantic difference in the stimulus material (Duncan et al., 2009).

Reality distortion, disorganization, and negative symptoms have been related to the abnormal N400 in schizophrenia (Andrews et al., 1993; Kostova et al., 2005; Debruille et al., 2007b). Nevertheless an altered self-concept and a disturbed inner integrity of the mental personality are seen as core symptoms of schizophrenia (Kraepelin, 1913; Parnas et al., 2005; Pauly et al., 2011). Ego pathology symptoms like thought insertion, delusions of being controlled or modified by an external force may lead to an experienced loss of individuality and sense of autonomy. Failures in very basal multisensory processing may be responsible for the subjective psychopathological symptoms (Kircher, 2008). Higher cognitive processes such as over attribution or the avoidance of cognitive dissonance may subsequently lead to a changed concept of self as well as metacognition of others. The aim of the present study is, to verify how the N400 is altered by judging the congruence of trait adjectives with the own self-concept and how it is associated with the severity of the underlying ego pathology.

In the present study subjects were engaged in a self-referential task described before by Esslen et al. (2008), as they were shown simple sentences written either in the first or in the third person describing a male or a female person with an adjective. The task was to decide whether or not the sentences describe the participant or a previously defined other well-known person correctly. The N400 is not only elicited by sentence endings that belong to related semantic categories, but also by those that are unexpected (Kutas and Hillyard, 1984). Hence, a stronger N400 should be generated with adjectives that are incongruent or unexpected compared to congruent adjectives. In our experiment the first two words of the sentence primed the context and therefore activated certain knowledge: subjects had to think either about themselves or about a close friend. According to the integration and inhibition theory of the N400 we expected little inhibition to be needed to integrate an adjective in a congruent sentence ending. In incongruent sentence endings we expected more integration effort which should result in more inhibitory processes. In summary, in healthy participants we expected the N400 to be more pronounced in the incongruent sentence endings compared to the congruent endings.

For the schizophrenia patients we hypothesized that they would exhibit a smaller than normal N400 effect (i.e. that the difference in the activation after an incongruent word is similar to the activation to a congruent word) in line with the view that the primary memory functional organization deficit in schizophrenia facilitates the integration of the unexpected and incongruent word.

Furthermore schizophrenia patients, who are affected in their inner self, e.g. experiencing ego pathology symptoms, might show a decreased so-called “self-reference effect”. In healthy subjects, the self-reference effect has been known for a long time and describes the phenomenon that information is differently encoded and better recalled when related to the self (Rogers et al., 1977; Symons and Johnson, 1997). Up to now, many studies investigated the neuronal basis of self-referential processing by giving subjects the task to evaluate the self-descriptiveness of personality traits while applying functional neuroimaging methods (for a review consider Northoff et al, 2006) or electrical tomographic techniques (Esslen et al., 2008). Studies that additionally collected behavioral reaction time revealed that self-relevant traits were evaluated significantly faster than self-irrelevant ones (Kircher et al., 2000; 2002; Kelley et al., 2002, Mcrae et al., 2004) and accordingly related it to the fact that healthy individuals have an elaborate and stable self-concept which serves to facilitate responses to self-relevant words (Kihlstrom, 1993; Maki and Carslon, 1993).

So far, only few studies have investigated this issue in schizophrenia. Pauly et al. (2011) were not collecting reaction time but found the amount of patients’ ego pathology symptoms to be negatively correlated with their recognition performance for previously self-referred traits. It could be hypothesized that firstly in schizophrenia patients a bias to a faster reaction time to self-relevant

words may not be observed and secondly, the N400 effect may be less pronounced as the "internal prime" of a stable self-concept (Kircher et al., 2000) is missing.

2. Methods

2.1. Subjects

16 schizophrenia patients and 16 healthy subjects participated in this study. Patients were recruited during their stay at the Psychiatric University Hospital Zurich. The study protocol was approved by the Ethics Committee of the canton Zurich. All participants gave written informed consent after receiving a detailed description of the study. All participants were right handed and German native speakers, had no history of alcohol, drug abuse or traumatic head injury and had no comorbid psychiatric disorder. Patients' symptomatology was assessed by a standardized semi-structured interview based on the AMDP system (Fähndrich and Stieglitz 2007), the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Postitive Symptoms (SAPS) (Andreasen, 1983; 1984). Based on the SANS and SAPS ratings, we calculated the scores for the psychotic, negative and disorganized factor (according to Miller et al. 1993). Depressive symptoms were assessed using the Hamilton Depression Scale (HAMD, Hamilton, 1960). An estimation of verbal crystalline intelligence was assessed by the German Mehrfachwahl-Wortschatz-Intelligenztest (MWT; Lehrl et al., 1995). Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971). All participants of the study were examined carefully by clinically skilled psychiatrists and psychologists. Table 1 displays the demographic characteristics of the included patients and controls. There were no significant differences between groups with regard to age, verbal intelligence or educational level. All patients received atypical antipsychotic medication at the time of the EEG recording, one patient additionally a typical antipsychotic and one additionally antidepressive medication. Patients mean daily antipsychotic medication in chlorpromazine equivalents was 668 mg (SD=348) (Andreasen et al., 2010).

--- *insert table 1 about here* ---

2.2. Procedures

Participants were shown 3-word German sentences, word by word, on a computer screen. They had to make a yes/no decision on the third word of each sentence. All third words were randomized trait adjectives in two different conditions: self-reference (SR) (e.g.

"I am happy") and other-reference (OR) ("She/He is happy"). In the SR condition participants were required to evaluate if the presented word was descriptive to themselves, and in the OR condition if it was descriptive to a close, pre-defined, well known friend or relative, though romantic relations were excluded. A total of 60 adjectives from the standardized German-Eigenschaftswortliste (EWL-K; Janke and Debus, 1978) were used. The adjectives describe a broad spectrum of mental and physical conditions. Thirty adjectives of each, positive and negative valence, were chosen. The trait adjectives were balanced between both conditions on basis of their number of syllables (positive: 2.63 +/- 0.62 SD and negative trait adjectives: 2.60 +/- 0.81 SD). Each word of the sentence was presented in the centre of a computer screen for 300ms followed by a fixation cross presented for 500ms. After the last fixation cross a question mark signaled the participants to evaluate the appropriateness of the adjective via button press (Yes/No) (Figure 1). Participants' answers and reaction times were collected.

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2.3. Data collection and analysis

A 32-channel EEG using BrainAmp system (BrainProducts, Germany) was recorded. The silver/silver-chloride electrodes were attached to the scalp with the help of an application cap (Easy Cap, Falk Minow Services, Germany), designed according to the international 10-20 system with FCz as recording reference. The digital sampling rate was 500 Hz and on-line filtering held between 0.1 Hz and 100 Hz (12 dB/octave rolloff each). The impedance was kept below 10 kOhm.

EEG analysis was performed using Brain electrical source analysis BESA software (version 5.3; Megis Gräfelfing, Germany). Prior to the averaging procedure the EEG data were filtered off-line with a low cutoff of 0.5 Hz (6 dB / octave each) and high cutoff of 30 Hz (24 dB / octave each). The EEG was re-referenced offline to an average reference. Individual trials containing artifacts due to eye movement, excessive muscle activity or amplifier blocking were rejected off-line by visual inspection before time-domain averaging. Mean percentage of trials lost to such artifacts was 14% for patients and 9% for controls.

The EEG data was segmented into fragments of 1000ms, which started 100ms before the stimulus of interest (the adjective) and ended 900ms afterwards. For each participant, separate ERP averages were

obtained for the SR and OR condition and for incongruent (trait adjective was not descriptive, participant answer therefore was “No”) and congruent trials (participant answer was “Yes”).

Although the N400 effect is already detectable at a single electrode, e.g. the midline central electrode site Cz (Rebai et al., 1997, Salisbury 2010b), most studies report a broad scalp distribution of N400 which is best observed at the recordings from the centro-parietal midline (Duncan et al., 2009; Kawohl et al., 2010; Kiang et al. 2012). In respect to this distribution we used not only a single electrode analysis with Cz but also pooled the electrodes Fz, Cz, Pz, F3/4, C3/4 and P3/4 in one channel for further analysis.

As the N400 component often does not form a clear peak but rather a negativity extended in time, average amplitudes of successive, overlapping 200ms long time intervals were analyzed (from 200ms to 700ms post-stimulus) as suggested by Munte (Munte and Heinze, 1994; Kawohl et al., 2010). A baseline correction was performed for each type of sentence and condition using the average amplitude from the interval -100ms to 0ms before stimulus onset. The N400 difference waveform (N400 effect) was calculated by subtracting the average ERP of the congruent condition from the incongruent condition.

2.4. Statistical analysis

Two sample t-tests were performed to compare the demographic data of the two groups. Kolmogorov-Smirnov test of normality revealed that all measures were normally distributed.

Reaction time was analyzed by separate repeated-measures analysis of variance (ANOVA) to assess the effects of the factors *group* (SZ patients and controls), *reference* (self- and other-reference) and *congruence* (congruent and incongruent). Additionally separate analysis for the response pattern (percentage of Yes/No answers) as well as repeated-measures ANOVA with the within-subject factors reference and valence and the between-subject factor group was performed. For the evaluation of the N400 amplitude a 2×2×2 repeated-measures ANOVA with the within-subject factors *reference* and *congruence* and the between-subject factor *group* was performed. Greenhouse-Geisser corrections for non-sphericity were applied. Finally, to investigate potential consequences of an altered self-perception on the N400 effect, correlations were calculated between psychopathological symptoms and the N400 effect in the SR condition at the specified time intervals. We further focused on SAPS items assessing positive symptoms affecting the self, such as thought broadcasting, thought insertion, ideas of reference or feeling of being controlled (SAPS items 14 to 19) and additionally grouped these for further analysis as “ego pathology” symptoms (M=3.7, SD=3.2). To control for a specific effect of ego pathology and to exclude a correlation with general severity of psychopathologic symptoms,

additional correlations were calculated using the negative, the psychotic and the disorganizes factor of the SAPS/SANS.

Correlation co-efficients were calculated wherefore Spearman's rank-order co-efficient ρ was used. The error probability was predefined as $p < 0.05$ (two tailed).

3. Results

3.1. Behavioral results

Results of the ANOVA revealed significant differences between groups concerning *reference* (F=4.3, df=1, 30, and P=0.045), *congruence* (F=10.0, df=1, 30, and P=0.004) and *response pattern* (F=6.2, df=1, 30, and P=0.018). Significant interaction effects were found for *reference* and *congruence* (F=5.8, df=1, 30, and P=0.02) and a trend for *reference* and *congruence* and *group* (F=3.43, df=1, 30, and P=0.07), as well as the trend for main effect group (F=3.51, df=1, 30 and P=0.07). Post hoc comparisons revealed that, controls were significantly faster in judging if a trait describes the self than if it describes a close friend (t=-3.5, P=0.001). In the schizophrenia group, the effects was not seen as patients were not faster judging the own traits than the traits of a well known person. Furthermore, they responded equally fast to incongruent as to congruent adjectives (all P>0.83). Looking at the reaction time depending on the valence of the traits, a significant main effect for *group* (F=5.33, df=1, 30 and P=0.02) was found and significant interaction effects for *congruence* and valence (F=9.88, df=1, 30, and P=0.004) and congruence and valence and group (F=4.37, df=1, 30 and P=0.04) were found. In healthy subjects the reaction time was shorter in congruent trials following a positive compared to a negative trait (t=2.64, P=0.01). All other comparisons revealed no significant characteristic response pattern, especially in patients the response time was similar following positive and negative, and incongruent and congruent trials respectively. Further, the analysis of the response pattern revealed that controls showed both in SR and OR conditions an equal response pattern (Yes-answers in SR: 47.6%, S.D. 9.0, in OR: 47.5%, S.D. 12.7, all P>0.27). Patients, however, more often agreed with a trait adjective in SR than denying it (Yes-answers: 55.7% S.D. 6.5, t=3.5, P=0.004). In the OR condition the responses were equal (Yes-answers: 49.1% S.D. 9.8, P>0.53). Examining the response pattern related to the valence of the traits, a significant main effect for reference was found (F=59.0, df=1, 30, and P<0.00) and for the interaction of reference and valence (F=4.8, df=1, 30 and P=0.03). Post hoc t-tests revealed that overall, positive traits were affirmed more often than negative traits (t=13.5, P<0.00) in reference to oneself as well as to a close friend. Thereby, schizophrenia patients and controls equally often affirmed the positive traits in self-reference. However, patients tended to a negative bias by characterizing themselves significantly more often with negative traits

(t=2.3, P=0.02). This attribution pattern was not correlated with patients severity of depressive symptoms rated on the HAMD (r=-0.10, P=0.71). Mean reaction time and response pattern are shown in Figure 2.

--- *insert figures 2 and 3 about here* ---

3.2 N400 components

Grand average ERPs for all conditions, for schizophrenia and control group, are shown in Figure 3. The repeated-measures ANOVA for the N400 amplitudes revealed within 300 to 500ms significant main effects for *reference* (F=4.82, df=1, 30, and P=0.03) and *congruence* (F=7.36, df=1, 30, and P=0.01) and a trend for the interaction of *congruence* and *group* (F=4.04, df=1, 30, and P=0.05). In the earlier time window from 200 to 400ms post-stimulus main effects for *reference* (F=7.08, df=1, 30, and P=0.01) and *congruence* and later from 400 to 600ms a main effect for *congruence* (F=4.82, df=1, 30, and P=0.03) as well as a trend for the interaction of *congruence* and *group* (F=3.02, df=1, 30, and P=0.09), subsequently from 500 to 700ms a main effect for *congruence* (F=5.03, df=1, 30, and P=0.03). Earlier or later time windows displayed no significant effects or interactions. Post-hoc LSD tests, performed to assess the differences between the N400 amplitudes for incongruent and congruent conditions, merely revealed significant differences in the control group, but not in the schizophrenia group. In the SR condition Controls showed a significantly larger negative deflection for incongruent than for congruent adjectives measured at the pooled electrode in the 400 to 600ms time window (t=-2.6, P=0.019). The effect was strongest at the central electrode Cz with significant time windows from 300 to 500ms (t=-3.01, P=0.009), 400 to 600ms (t=-3.9, P=0.001) and a trend from 200 to 400ms (t=-2.07, P=0.055).

The analysis of the N400 amplitude in the other reference (OR) condition revealed no significant effects. Although the schizophrenia patients generally showed larger N400 amplitudes to incongruent endings, the N400 effect (incongruent minus congruent) was smaller than in the controls. Neither in the self- nor in the other-reference condition did the ERP waveform elicited by the incongruent trait adjective differ significantly from the ERP elicited by the congruent adjective (all P>0.14).

3.3. Clinical correlations

Since the N400 has a negative amplitude, positive correlation co-efficients indicate that the N400 effect was smaller with higher symptom ratings. High scores in the ego pathology sum score (see above) were correlated with a significantly smaller N400 effect (r=0.51, P=0.044) at the 300 to 500ms

interval in the self-reference condition. In addition there was a weak correlation between "ideas of reference" (SAPS item 14, r= 0.492, P=0.053) and "delusions of mind reading" (Saps item 16, r=0.488, P=0.055) with a reduced N400 effect at 300 to 500ms as well as later a trend at 600 to 800ms ("thought withdrawal", r=0.455, P=0.077). The scores of the psychotic, negative and disorganized factor were not correlated with the N400 effect (Table 2).

Further analyses were performed to determine possible drug effects on N400 effect. No correlations were found between the medication (chlorpromazine-equivalent doses) and N400 effect (all P>0.13).

--- *insert table 2 about here* ---

4. Discussion

In schizophrenia patients, the N400, an index reflecting the integration of a given word in the concomitant context, is frequently altered. The aim of the present study was to investigate, if an altered N400 can also be found in semantic violations of the own self-concept. The analysis of the total group revealed a significant classic N400 effect with more negative N400 during processing of incongruent stimuli compared to congruent stimuli. As hypothesized,

post-hoc analysis confirmed that this effect only occurs in the control group and not in the schizophrenia patient group.

Moreover, healthy controls were faster in judging the appropriateness of the trait adjectives in the self- compared to the other-reference condition. As expected, neither the N400 effect after incongruent and congruent traits nor the behavioral response bias could be detected in the schizophrenia group. Interestingly, the higher the patients scored in ego-pathology symptoms, the smaller the N400 effect turned out to be.

Up to now, only few studies investigated N400 related processes induced by evaluation of trait adjectives. A study with a similar design found comparable to our findings in healthy subjects increased negative N400 over fronto-central scalp locations for self-negative words compared to self-positive ones (Watson, 2007). In the current study, an N400 effect could not be observed in the patients group. This may be explained with disturbed attention and memory processes caused by aberrant salience (Kapur, 2003; Kapur et al., 2005). Deficits in the suppression of attention directed towards irrelevant or familiar stimuli, or in other words, excessive attention to information that is irrelevant or already highly familiar, leads to aberrant salience of objects and associations. In

schizophrenia aberrant salience has been linked to failure of suppression of irrelevant stimuli on behavioural or cognitive level (Morris et al., 2012) or weakening of contextual constraint (e.g. *theory of mind* (Uhlhaas et al., 2006); *N400* (Kiang et al., 2008); for review see Nelson et al., 2013). Keefe and colleagues (2009) have recently introduced a "memory prediction" model of cortical function which helps to explain the slowed and more effortful processing of incoming information and the increase of randomly, internally oriented interpretation of stimuli. According to this model, common and usually automatic processed stimuli become unfamiliar due to failings in "top-down" processes (ability to "fill the gaps") and flagged for more deliberate analysis by higher cortical areas. Likewise it may be assumed that in schizophrenia the reduced N400 following unexpected stimuli may be an expression of this. Aberrant salience would thus cause attention shifts to familiar or "irrelevant" stimuli which disturbs the pre-reflective and automatic processing of various aspects of self-experience (Nelson et al., 2013).

Moreover in schizophrenia, deficits in activating concepts related to a meaningful prime may cause more negative N400 amplitudes to contextually *related* targets (Kostova et al., 2005; Kiang et al., 2012) and/or less than normal N400 relatedness priming effects, resulting in an overall reduced N400 effect (difference waveform between N400 to unrelated (incongruent) and related (congruent) concepts) (Ohta et al., 1999; Ditman and Kuperberg, 2007). According to a recent fMRI study the posterior cingulate cortex and precuneus seem to be the underlying brain areas, in which schizophrenia patients and controls show differential activation in the self-referential task (van der Meer, 2012).

However, the smaller or missing N400 effect in schizophrenia can be due to alterations at different points of the information processing system. Deficits in context processing or maintenance as well as verbal working memory decay have been connected with the lack of the N400 effects in schizophrenia (Kostova et al., 2005; Salisbury, 2010a; Salisbury, 2008; Sitnikova et al., 2002). Since the context in our experiment is not strictly defined but "needs to be imagined", it is possible that the patients had difficulties fulfilling the experimental task and had problems utilizing the activated semantic representations of "I", "he" and "she" the same way the healthy subjects did. If so, this would prevent the normal spread of activation in semantic memory networks of the prime concept. Kiang et al. (2012) on the contrary found in their study that more than an inability to activate the prime concept, the altered N400 may be due to abnormal functional connections of the semantic memory.

Kreher et al. (2009) showed a reduced direct and indirect N400 priming effect in schizophrenia patients after implementing a semantic decision making in the task. That way, in the implicit task, patients with schizophrenia showed normal or even increased N400 effects by the heightened automatic spread of activation within semantic memory. In the explicit task instruction, subjects were

required to explicitly match prime and target, the same way it was required in our study. In the schizophrenia group, this resulted in decreased N400 effects. They therefore suggested that a failure to mobilize semantic search strategies may be responsible for the lack of the usually observed abnormal increase in automatic spreading activation in schizophrenia patients.

In our study, reaction time analysis revealed that controls responded faster in the self- than in the other-reference condition which might be explained with processes related to the self-reference effect (Rogers et al., 1977; Kihlstrom, 1993; Maki and Carslon, 1993). In the patients with ego pathologies the reaction time advantage was not found, likely due to the absence of a stable and elaborate self-concept. In healthy subjects the reaction time was shorter in congruent trials following a positive compared to a negative trait. Likewise Watson et al. (2007) found in a task, were subjects had to judge the self-referential content of positive and negative words, the reaction time to be shorter in self-positive words.

The analysis of the response pattern depending on the valence of the personality traits revealed that subjects ascribed overall more positive than negative traits to themselves. This is in line with the finding that individuals show a tendency to attribute positive events to internal causes resulting in a overly positive view of themselves ("self-serving bias") (Blackwood et al., 2003; Fraguas et al., 2008; Pauly et al., 2011). The close other was thereby equally generously rated than the self. However, schizophrenia patients tended to a negative bias by characterizing themselves significantly more often additionally with negative traits than controls did. This resulted in a different response pattern in the schizophrenia group with markedly more Yes-answers (positive and negative traits) in the self-reference condition which could be an expression of an increased self-attribution in schizophrenia. An alteration in the attribution of salience to stimuli is discussed to be related to the dysregulation of dopaminergic neurotransmission in schizophrenia (Kapur, 2003; Roiser et al., 2009; Esslinger et al., 2012).

Nevertheless, perhaps the clinically most interesting finding of our study is the correlation between the manifestation of ego pathologies and the N400 effect. This leads to the assumption that there may be a connection between a disordered self-concept (manifested by the existence of ego pathology symptoms) and the disturbed semantic processing as indexed by the N400 effect. In general, smaller N400 amplitudes are thought to reflect less intense integration efforts. The interpretation of Debruille (2007a) may be helpful; he assumes that an integration deficit is responsible for the small N400 in patients and not less intense integration efforts. Thus, the integration deficits may be more pronounced the more severe the ego pathology symptoms are. Furthermore, it could be speculated that the integration deficit is partly responsible for the persistence of ego pathology symptoms. This integration deficit may result in a disturbed representation and evaluation of the subject's experiences

of the environment. From a neurobiological view it is assumed that this representation and evaluation is necessary to create a coherent self-concept.

This study has some limitations. Even though the schizophrenia patients and the healthy controls were matched based on age, education and IQ, first the modest sample size must be taken into consideration, and second the fact that the patients group contained more male subjects than the control group which might have influenced the results. Moreover, the schizophrenia group was heterogeneous based on the type and amount of administrated medication. Although an influence of medication on the N400 amplitude has rarely been reported (Condray et al., 2009), it cannot be excluded. Word frequency and length was controlled in self- and other-reference trials as it can affect the N400 amplitude. However, the composition of traits classified as congruent or incongruent naturally varies between subjects and therefore a possible influence on the N400 amplitude cannot ultimatively be excluded.

Despite these limitations, the results obtained in this study deliver interesting discussion points and give possibilities for further research. In summary, the missing N400 effect in schizophrenia is probably associated with a disordered self-concept in the patients.

Table 1
Demographic and clinical characteristics of the study sample (means ± S.D. given where applicable).

	Schizophrenia patients	Healthy subjects	F, t or X^2	P
N	16	16		
Age, years	29.0 ± 6.7	27.9 ± 9.3	$0.39_{(30)}$	0.69
Sex (male/female)	13 / 3	8 / 8	$3.4_{(1)}$	0.07
Education, years	13.0 ± 1.7	14.2 ± 1.9	$1.78_{(30)}$	0.12
Verbal IQ	105.4 ± 12.1	112.9 ± 13.3	$1.5_{(30)}$	0.13
SAPS total	7.9 ± 4.9			
SANS total	9.1 ± 3.8			
Negative factor	5.6 ± 2.6			
Psychotic factor	4.6 ± 1.9			
Disorganized factor	2.3 ± 1.2			

Table 2
Correlation coefficients of psychopathological rating and N400 effect at the pooled electrode. Earlier and later time window do not show significant effects.

Time Window	Ego pathology		Negative factor		Psychotic factor		Disorganized factor	
	r	P	r	P	r	P	r	P
300 – 500 ms	0.51*	**0.04**	-0.25	0.34	0.35	0.17	-0.40	0.12

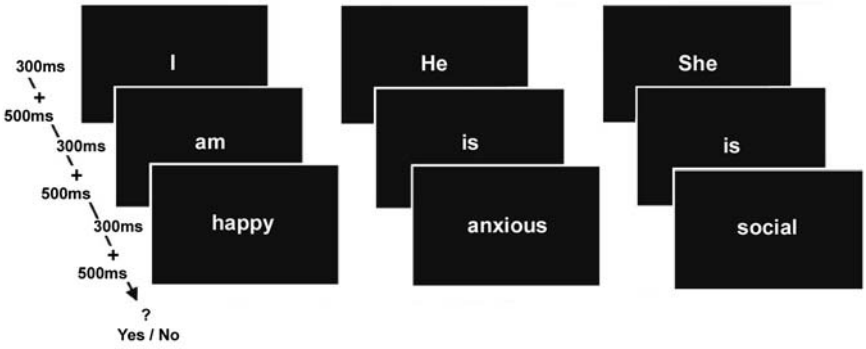

Figure 1

Schematic illustration of self- and other-reference in the study paradigm. All words were in German**.**

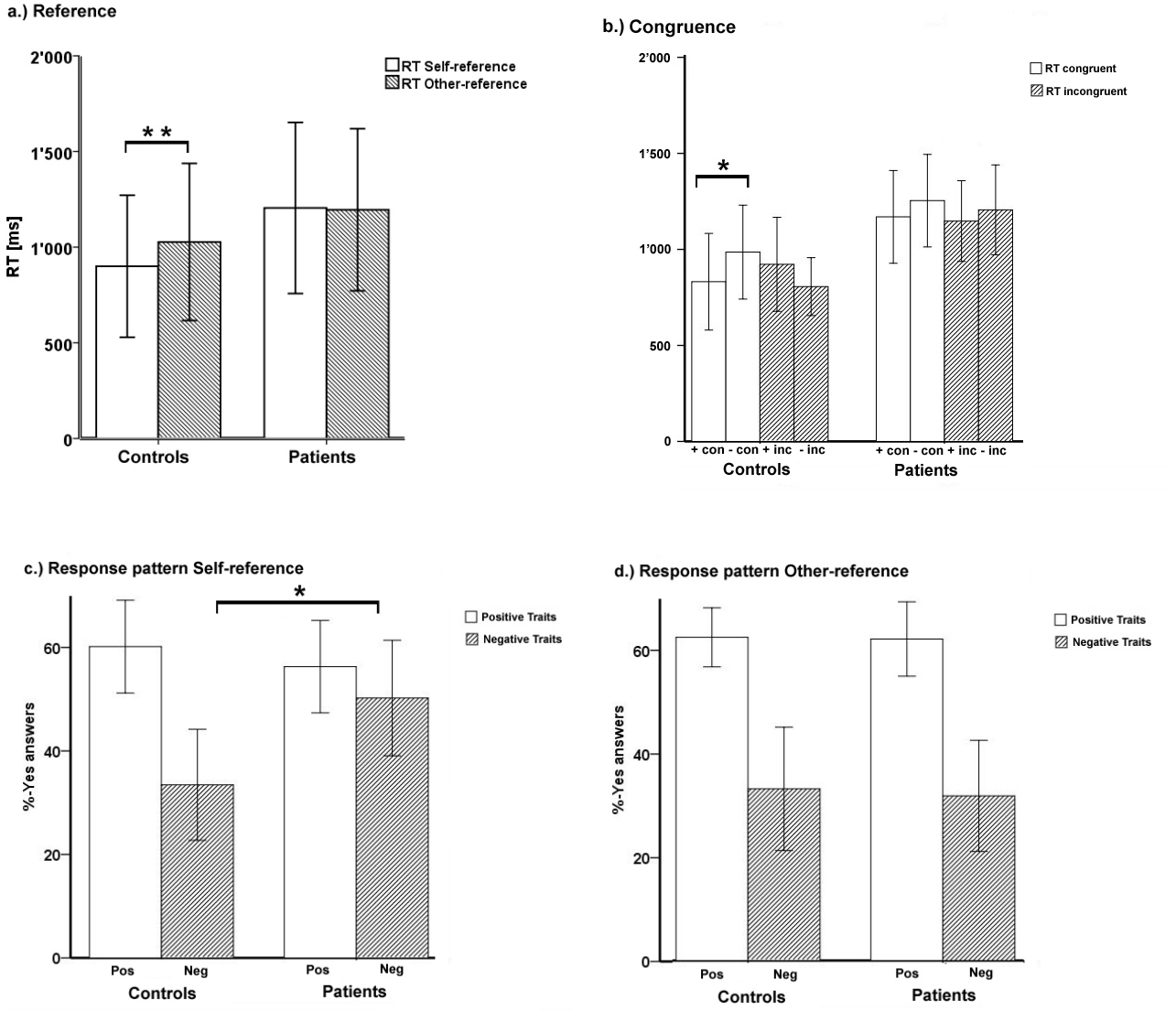

Figure 2

a.) Mean reaction time in the self-reference (SR) compared to the other-reference (OR) condition. **Controls respond overall faster in self-reference (*P*=0.001). b.) Self-reference: mean reaction time in congruent and incongruent trials, and in relation to valence of traits. *Controls respond faster in congruent trials following a positive compared to a negative trait (*P*=0.01). c.) Percentage of Yes answers in SR and d.) in OR. *Patients characterized themselves significantly more often with negative traits (*P*=0.02), displaying therefore overall more Yes-answers in the SR condition (*P*=0.004).

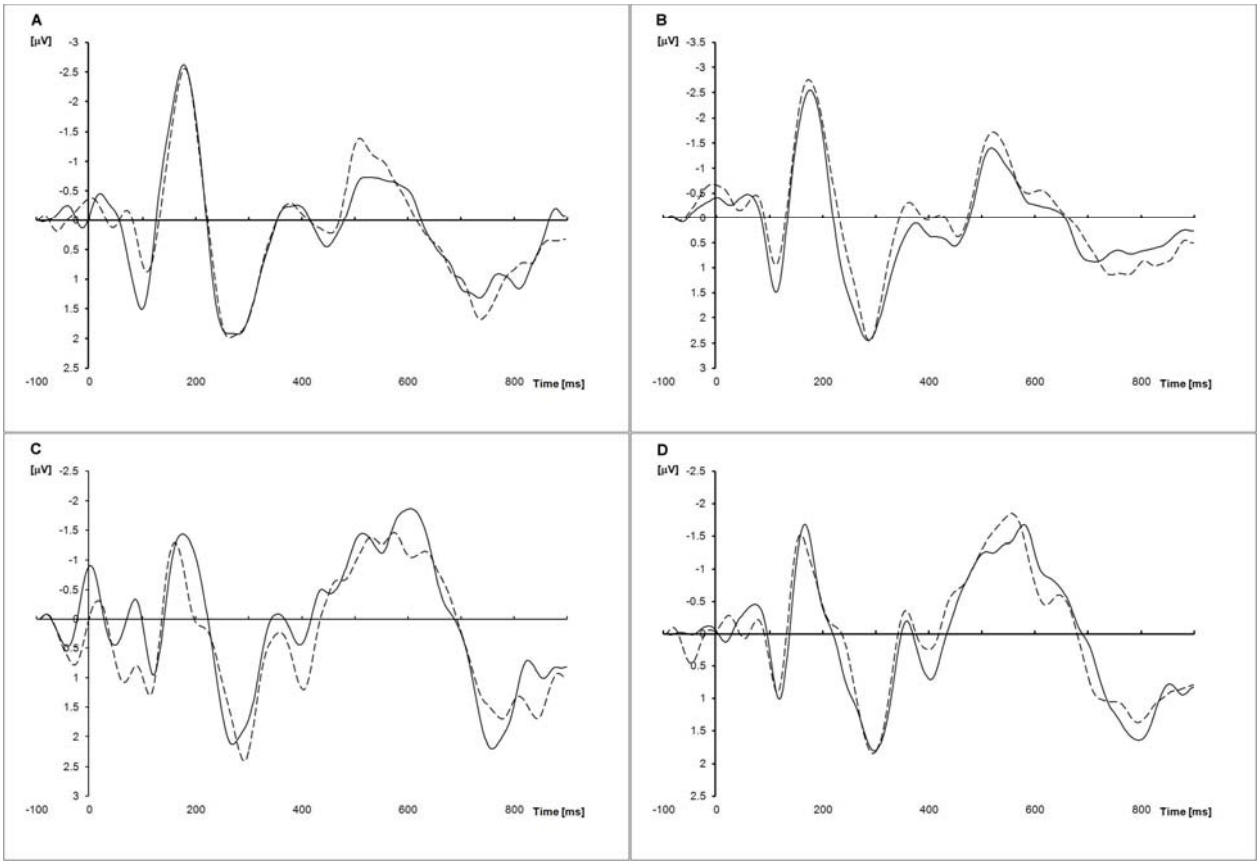

Figure 3

Grand average ERPs (pooled electrode). A: SR in controls. B: OR in controls. C: SR in schizophrenia patients. D: OR in schizophrenia patients. Dashed line: incongruent adjectives; Continuous line: congruent adjectives.

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6.2 Study II: Neurocognitive profiles in help-seeking individuals: Comparison of risk for psychosis and bipolar disorder criteria.

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ABSTRACT

BACKGROUND: Neurocognitive deficits are important aspects of the schizophrenic disorder because they have a strong impact on social and vocational outcomes. We expanded on previous research to focus on the neurocognitive profiles of persons at High-Risk (HR) or Ultra-High-Risk (UHR) for schizophrenic and affective psychoses. Our main objective was to explore whether neurocognitive measures are sufficiently sensitive to predict a group affiliation based on deficits in functional domains.

METHODS: This study included 207 help-seeking individuals identified as HR (N=75), UHR (N=102), or at high risk for bipolar disorder (HRBip; N=30), who were compared with persons comprising a matched, healthy control group (CG; N=50). Neuropsychological variables were sorted according to their load in a factor analysis and were compared among groups. In addition, the likelihood of group membership was estimated using logistic regression analyses.

RESULTS: HR and HRBip participants performed both comparable and intermediate levels between controls and UHR. The domain of processing speed was most sensitive in discriminating HR and UHR [odds ratio (OR) 0.48; 95% confidence interval (CI) 0.28-0.78, p=0.004] while learning and memory deficits predicted a conversion to psychosis (OR 0.47; 95% CI 0.25-0.87, p=0.01).

CONCLUSIONS: Performances on neurocognitive tests differed among our three at-risk groups and may therefore be useful in predicting psychosis. Overall, cognition had a profound effect on the extent of general functioning and satisfaction with life for subjects at risk of psychosis. Thus, this factor should become a treatment target in itself.

Keywords

Clinical high risk/prodrome/cognition/neuropsychology/psychosis/bipolar

1. Introduction

Neurocognitive deficits are an important aspect of the schizophrenic disorder. They may determine social and vocational outcomes even more than do psychopathological symptoms. Environmental factors and social adjustment, e.g., the level of isolation or ability to function outside the nuclear family, are predictors of a first psychosis in subjects at ultra-high risk (Dragt et al., 2011). Because the capacity to process socially relevant information also relies on basic neurocognitive abilities (i.e., attention and memory), deficits in those domains may strongly influence the social embedment and ability to cope with early psychotic symptoms (Green et al., 2000). According to the neurodevelopmental hypothesis of pathogenesis in schizophrenia, as well as recent findings, neurocognitive deficits are most likely to be present prior to the manifestation of full-blown schizophrenia (Giuliano et al., 2012). This supposition is also supported by a recent large population study of young Swiss conscripts. There, Müller et al. (2013) found significantly frequent evidence of cognitive impairments early in life for individuals who were later diagnosed with schizophrenia. Therefore, an assessment of cognitive functioning should be taken into account in early detection of psychoses. Because impairments can be quantified before the onset of the illness, researchers have proposed using them as an additional indicator when optimizing one's prediction of psychosis risk (Riecher-Rössler et al., 2009; 2013). Moreover, to create useful interventions in the pre-psychotic phase, it is essential that we learn more about deficits during this early stage of illness so that we can identify individuals truly in need of help and provide appropriate intervention.

Yung and McGorry (1996) conceptualized the ultra-high-risk (UHR) criteria, which indicate the imminent transition to schizophrenia. These criteria include the manifestation of attenuated positive symptoms (APS), brief intermittent psychotic symptoms (BLIPS), or a state–trait component that combines vulnerability with a distinct reduction in global functioning within the past year. The basic symptom concept of Huber (1966) involves a putative, even earlier, at-risk state – defined here as a high-risk (HR) criterion – in which help-seeking individuals mainly describe the disturbing experience of subtle and self-reported alterations and deficits observed in cognition, thoughts, and perception (Klosterkotter et al., 2001). The continuum model of psychosis underlying these at-risk studies emphasizes the many similarities across different psychotic diagnostic categories. However, these disorders also have important differences. This is especially true for affective psychoses (depression with psychotic features or bipolar disorder with psychotic features) versus schizophrenic psychoses (schizophrenia, schizophreniform disorder, or schizoaffective disorder). Here, we introduce a high-risk-for-bipolar component in order to investigate those overlaps and contrasts between affective and schizophrenic psychoses. For this, help-seeking individuals with prominent depressive and/or manic symptoms, but who did not meet the HR or UHR criteria, were classified as high-risk bipolar (HRBip).

Recent meta-analyses of the at-risk state for schizophrenic psychosis have confirmed that impairments in neuropsychological performance (Fusar-Poli et al., 2012; Giuliano et al., 2012), alterations in brain structure (Mechelli et al., 2011; Fusar-Poli, 2012), social cognition (Fusar-Poli et al., 2010), and general functioning and neurochemistry (Smieskova et al., 2013) are associated with a clinically high risk (Addington and Heinssen, 2012; Fusar-Poli et al., 2013). Studies of cognition in at-risk individuals have found small to medium impairments across most neurocognitive domains that are at an intermediate level between those of healthy individuals and subjects diagnosed with schizophrenia (Hawkins et al., 2004; Brewer et al., 2006; Pukrop et al., 2006; Eastvold et al., 2007; Fusar-Poli et al., 2012). Moreover, individuals at risk who later convert to psychosis show more severe baseline neurocognitive deficits in almost all domains when compared with non-converters, especially for processing speed, verbal fluency, and memory (Pukrop and Klosterkotter, 2010; Giuliano et al., 2012). To our knowledge, only a few studies have directly compared putative HR (defined by basic symptoms) and UHR psychosis groups. For example, Frommann et al. (2011) identified an executive control impairment in the early (HR) state but additional memory dysfunction in the late (UHR) prodromal state. Simon et al. (2007) reported equivalent neurocognitive performances in subjects meeting basic symptom or UHR criteria.

Research on clinical and neurobiological markers in help-seeking individuals at risk for progression to bipolar disorder is still limited and inconsistent (Bechdolf et al., 2012). An earlier prospective birth cohort study found early in the developmental course of the disorder impairments in tasks that involve psychomotor speed as well as attentional and executive abilities (Cannon et al., 2006). However, this was true only for subjects who later developed a schizophrenic disorder but not for individuals who subsequently developed an affective disorder. Therefore, the authors concluded that early motor and attentional or executive impairments may be specific to schizophrenia-related rather than affective disorder outcomes. Ratheesh et al. (2013) reported lower global functioning in at-risk subjects who converted to bipolar disorder than in those who did not, although differences in neurocognitive characteristics could not be detected. Conversely, a literature review by Olvet et al. (2013) suggested that deficits in specific neurocognitive domains, such as verbal memory and executive function represented potential predictors of bipolar disorders. Therefore, investigating the nature of deficits and symptoms in individuals with an increased risk of developing an affective or schizophrenic disorder might provide further insight into the neuropathophysiological mechanisms underlying both illnesses.

Our study objectives were to explore the neurocognitive functioning in an at-risk population and to determine whether neurocognitive measures are sensitive enough to differentiate among HR, UHR, and HRBip individuals. This examination expanded upon previous research by addressing the neurocognitive functions and clinical characteristics of persons at high and ultra-high risk of schizophrenic psychosis, subjects at-risk for bipolar disorder, and a group of matched, healthy

controls. Accordingly, we hypothesized that 1) HR and UHR subjects exhibit generalized neurocognitive deficits compared with the control group, 2) deficits in measures of learning and memory are associated with more severe psychopathological symptoms, and 3) persons within the HRBip group have fewer deficits in their psychomotor speed-dependent tasks than do those in either the HR or UHR group.

2. Methods

2.1 Subjects

Individuals were recruited within the context of a study on early recognition of psychosis (ZInEP; in German: Zürcher Impulsprogramm zur nachhaltigen Entwicklung der Psychiatrie, www.zinep.ch) from the canton of Zurich, Switzerland. Potential participants had either learned about this study from a project website, flyers, or newspaper ads, or else were referred to our staff by general practitioners, school psychologists, counselling services, psychiatrists, or psychologists. All subjects spoke proper German and had normal or corrected-to-normal vision, normal hearing, and normal motor limb function. Those 18 years and older provided informed consent, while minors (<18 years) gave assent in conjunction with parental informed consent. The study was approved by the Ethics Committee of the canton Zurich and was carried out in accordance with the Declaration of Helsinki.

The ZInEP early recognition of psychosis project included 221 subjects in total. Complete neuropsychological data were available from 207 participants who fulfilled the criteria (see psychopathological assessment below) for either High-Risk (HR, N=75), Ultra-High-Risk (UHR, N=102) or at-risk Bipolar (HRBip, N=30). For comparison, 50 healthy persons, comprising our control group (CG), were recruited by advertising in the local newspaper or through word-of-mouth. Their qualifying data had suggested they were comparable in verbal intelligence, level of education, and gender to persons in the other groups. Exclusion criteria for study participation were manifest schizophrenic, substance-induced, or organic psychosis; current substance or alcohol dependence; or an estimated verbal IQ <80. Controls were screened with the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) based on DSM-IV criteria to exclude persons with any past or present psychiatric, neurological, or somatic disorder that might bias their cognition. None of the controls used psychotropic medication or illicit drugs. Demographic and clinical data of the study groups are displayed in Table 1.

2.2 Psychopathological assessment

To qualify for inclusion, participants fulfilled at least one of the following requirements.

1) HR: high-risk status for psychosis, as assessed by the Schizophrenia Proneness Interview, SPI-A (Adult version) or SPI-CY (Children-Youth version) (Schultze-Lutter et al., 2007; Schultze-Lutter and Koch, 2009), having at least one cognitive-perceptive basic symptom or at least two cognitive disturbances.

2) UHR: ultra-high-risk status for psychosis, as rated by the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003), having at least one attenuated psychotic symptom, or at least one brief limited intermittent psychotic symptom, state–trait criterion (reduction in global assessment of functioning (GAF; Endicott et al., 1976) of >30% in the past year, plus either a schizotypal personality disorder or a first-degree relative with psychosis).

3) HRBip: high risk for bipolar disorder, as defined by a score either ≥14 on the Hypomania Checklist (HCL), a self-report measure of life-time hypomanic symptoms (Angst et al., 2005); or ≥12 on the Hamilton depression scale (Schutte and Malouff, 1995), and not meeting any of the at-risk psychosis inclusion criteria listed above.

Quantitative measures of psychopathology were further obtained as follows: psychotic symptoms (Positive and Negative Syndrome Scale, PANSS; Kay et al., 1987), current axis-I comorbidity via MINI (Sheehan et al., 1998), general functioning per GAF (Endicott et al., 1976), and satisfaction with their psychosocial domains of life (Manchester Short Assessment of Quality of Life, MANSA) (Priebe et al., 1999). This assessment was conducted by trained, experienced psychiatrists or psychologists.

2.3 Neurocognitive assessment

A set of well-established neuropsychological tests was administered in a fixed order. Testing and scoring were performed blind to diagnostic status. The tests were chosen on the basis of their demonstrated reliability and capacity to discriminate clinically high-risk subjects from healthy controls. Verbal IQ was estimated with a German word recognition test (MWT-B; Lehrl, 1989) for adults or a test of receptive vocabulary for minors (PPVT; Dunn and Dunn, 2003). For the purposes of data reduction and examining generalized and specific deficits across cognitive domains, we grouped the test variables according to neuropsychological conventions (Table 2).

2.4 Statistical analysis

Demographic and clinical characteristics were compared between groups, using Chi-square and Fisher's exact tests for categorical variables or one-way ANOVAs with a Bonferroni post hoc test for continuous variables. Using Missing Value Analysis, we first identified subjects with more than three missing values on neurocognitive measures and excluded them from further analysis. Test scores were

standardized by computing z-scores based on the performance of the control group. Cognitive domain scores were calculated by averaging the z-scores on contributing variables. We then applied a factor analysis with varimax rotation and an eigenvalue cutoff of '1' to extract five factors that explained 69% of the total variance (Supplementary Table 1). Those factors represented the independent cognitive domains of speed, attention, learning and memory, working memory, and fluency. Measures of the planning/categories domain were excluded from further analysis because they operationalized higher and more complex executive functions, with high cross-loadings on most factors. Afterward, we conducted repeated-measures ANOVA to compare the cognitive profiles among groups. Univariate ANOVA was performed for individual domain scores. Chlorpromazine equivalents (Andreasen et al., 2010) and age were added as covariates in all models. Subsequent logistic regression models were used to estimate the probability of group membership with variables that had been proven significantly different in bivariate analysis, i.e., UHR versus HR; and converters versus at-risk psychosis (HR and UHR), based on their given deficits in functional domains. We then calculated Odds ratios (ORs) and 95% confidence intervals (95% CIs). Finally, to detect any associations between overall symptom severity of positive/negative symptoms and cognitive domains, we determined the partial correlation coefficients by controlling for age and neuroleptic medication. To reduce the bias inherent to multiple testing, we restricted those correlations to cognitive domains, as well as scores for PANSS, GAF, and the total for MANSA. All analyses were conducted using SPSS 20.0.

3. Results

3.1 Demographic and clinical characteristics

Based on their demographic and clinical characteristics, the participants within all groups were found to be comparable in their verbal/intellectual functioning, level of education, and gender (Table 1). However, persons were significantly younger in the UHR group than in the HR and HRBip groups. Although basic symptoms were common in both schizophrenic at-risk states of HR and UHR, the three at-risk groups differed significantly in terms of the severity of their positive, negative, and depressive symptoms as well as their level of general functioning. By contrast, all had equivalent affective symptoms, based on HCL ratings, and equivalent neuroleptic medication. By one year after completing the initial assessment, 15 of the 177 HR or UHR subjects (8.4%) had converted to psychosis while four had converted to a bipolar disorder.

3.2 Neurocognitive domains

The neuropsychological profiles for the three at-risk groups are displayed in Figure 1. Table 3 summarizes the results of the one-way ANOVAs, which contrasted the performances of individuals in

those groups with healthy CG persons, based on z-scores adjusted for age. Our comparison of cognitive domain factors between HR/UHR subjects and the CG revealed that at-risk-for-psychosis subjects were impaired in all domains (all p>0.01), with effect sizes (z-scores) ranging from –0.87 to –1.27 for UHR and from –0.33 to –0.78 for HR. Scores for HRBip subjects were quite comparable to CG members in the domains of attention (F=2.86, trend *p*-value=0.095) and learning/memory (F=3.21, trend *p*-value=0.077). The UHR group performed markedly worse than HR in the domains for speed (F=9.01, $p<0.001$), attention (F=5.99, $p=0.003$), working memory (F=3.66, $p=0.028$), and fluency (F=6.20, $p=0.003$). The two at-risk groups (HR versus UHR) scored rather low in the domains of learning/memory (F=1.67, $p=0.19$). When compared with the HRBip participants, those in the two at-risk-for-psychosis groups were markedly worse in the domains for speed (F=12.05, $p<0.001$), fluency (28.31, $p<0.001$), attention (F=13.50, $p<0.001$), and working memory (F=17.52, $p<0.001$) but not for learning and memory (F=0.60, $p=0.43$). The direct comparison of HR versus HRBip produced no significant differences in any category (all $p<0.10$). To control for depressive symptoms, we conducted a post hoc series of ANOVAs, using that factor as an additional covariate but finding no significant change in the results (data not shown).

Logistic regression models demonstrated that the domain of speed was negatively associated with being classified as UHR (versus HR; OR=0.48; 95%CI), whereas the other domains did not predict group membership (Table 4). That is, a poor result in the speed domain was linked to an increased likelihood of being classified as UHR. A second analysis focusing on the subgroup of individuals who ultimately converted to psychosis indicated that it was possible to identify clearly those converters within the HR and UHR groups based on their scores in the domain of learning and memory. Accordingly, learning/memory were negatively associated with a conversion to psychosis (OR=0.47; 95%CI).

3.3 Correlation with psychopathological symptoms

Among the at-risk-for-psychosis subjects, scores along the PANSS positive symptom scale were negatively associated with speed (r=–0.21, $p<0.001$), learning/memory (r=–0.32, $p<0.001$), and working memory (r=–0.21, $p=0.003$). Scoring along the negative symptom scale was negatively associated with speed (r=–0.16, $p=0.028$), learning/memory (r=–0.26, $p<0.001$), and fluency (r=–0.21, $p=0.003$). GAF scores were positively associated with the domain of working memory (r=0.20, $p=0.01$). Measures of attention were significantly associated with the MANSA total score (0.24; $p=0.037$). The HRBip group scores along the PANSS negative symptom scale were negatively associated with the learning and memory domain (F=-0.51, $p=0.004$). We also confirmed the correlation between working memory and general functioning for HRBip (r=0.42, $p=0.021$) as well as the association of attention with the MANSA total score (0.16, $p=0.036$). No other association was

proven significant, and depressive symptoms in particular were not correlated with any cognitive domain.

4. Discussion

We analyzed the neurocognitive performance of subjects at risk for schizophrenic or affective psychosis. Our goal was to determine whether our three psychopathologically defined risk groups could be distinguished based on their neuropsychological profiles. Three main findings emerged. First, for all domains, the three at-risk groups were impaired relative to the control group. Here, persons in HR or HRBip groups had comparable scores that were intermediate between the control and UHR members. Second, among subjects at risk for psychosis, their performance in the speed domain predicted a group affiliation of UHR while learning/memory deficits predicted a transition to psychosis. Third, neuropsychological deficits had a profound effect on an individual's level of general functioning and satisfaction with life.

As we had hypothesized, all groups differed from healthy controls in their neuropsychological functioning after controlling for age, gender, IQ, and neuroleptic medication. This indicated that their impairments were not simply a general intellectual deficit. Our findings are consistent with those from previous studies that examined individuals equivalent to our UHR subjects (Hawkins et al., 2004; Brewer et al., 2005; Lencz et al., 2006; Eastvold et al., 2007; Pflueger et al., 2007) as well as those involving persons with basic symptoms (Pukrop et al., 2006; Simon et al., 2007; Frommann et al., 2011). Profiles were quantitatively similar between our HRBip and HR subjects. However, in HRBip deficits were less pronounced, albeit not significantly, in the domains of attention and learning/memory. As with the results reported by Thompson et al. (2003), we found no putative prodrome features that clearly distinguished between HR and HRBip. Therefore, we could not prove our hypothesis that members of the HR psychosis group would show quantitatively more-severe deficits in the speed domain when compared with those in the HRBip group.

Regression analysis revealed that, within the at-risk-for-psychosis group (HR and UHR), a poor result in the speed domain was the most reliable predictor of an affiliation to the late UHR state. Other researchers have also determined that psychomotor speed is more consistent (Kelleher et al., 2012; Seidman et al., 2010) than reported (non speed-dependent) deficits in working memory and executive functioning (Gschwandtner et al., 2006; Hawkins et al., 2004; Keefe et al., 2006; Niendam et al., 2006; Pukrop et al., 2006). The cognitive processes and variables loading on our factor "speed" were the same as those utilized in the MATRICS consensus test battery "speed of processing" (Green and Nuechterlein, 2004). These involve perceptual and motor components, all emphasizing speed of performance. In accord with results described by Kelleher et al. (2012), our findings demonstrated that processing speed is a central deficit associated with risk. Moreover, from a multi-level assessment

of subjects at risk for psychosis, Riecher-Rössler et al. (2013) have shown that, in addition to psychotic (suspiciousness) and negative symptoms (anhedonia/asociality), a reduced speed in information-processing can heighten one's overall prediction to transition by up to 80.9%.

Our data further support the hypothesis that the at-risk state of psychosis is characterized by "systems"-based abnormalities, thus reflecting impairments in the processes of integration and coordination between distributed networks (Dickinson, 2008) rather than deficits in particular prefrontal and temporal lobe regions. Likewise, we found in the at-risk-for-psychosis sample of the ZInEP study that the inter-network-connectivity of the default mode with the task-positive network is significantly associated with the time required to solve the problem of the Tower of Hanoi task. In addition, as the complexity of the problem increases (i.e., from four-disk to five-disk tower), that association is strengthened (Wotruba et al., accepted). That is, the cognitive deficit seen in those at-risk subjects can be linked to an observed loss of antagonism in the task-positive and default mode network. This network is thought to reflect the competition between external and internal information-processing, and, as proposed by Wotruba et al., this may trigger a confusion of internally and externally focused states, enhancing one's vulnerability to a psychotic distortion of reality.

The classification of HR versus UHR is based on the assumption that symptom severity increases more or less linearly as a person progresses through the prodromal phase (Klosterkotter et al., 2011; Fusar-Poli et al., 2013). Whether one's neuropsychological impairments develop along a similar trajectory is not clearly understood. Green et al. (2000) have suggested that those impairments might already be present at a very early age, manifested by neurodevelopmental abnormalities, and might possibly increase with successive stages of prodromal symptomatology. Likewise, Frommann et al. (2011) have compared between members of HR and UHR groups and found executive deficits in subjects who had only basic symptoms as well as memory deficits in subjects who fulfilled the UHR criteria. In our study, a general impairment was observed with rising degree from HR to UHR. This suggested a parallel and interconnected development of neuropsychological deficits and observed psychiatric symptomatology. Confirming this hypothesis, we noted that the measures of speed and learning/memory were inversely associated with both positive and negative symptoms. Working-memory performance was associated with positive symptoms, whereas performance in fluency tasks was linked with the severity of negative symptoms. Regression analysis further revealed that, overall, the actual converters could clearly be distinguished from all other at-risk subjects because of a diminished performance in their learning and memory domain. Accordingly, a meta-analysis by De Herdt et al. (2013) has shown that performance in learning/memory can be differentiated between psychosis converters and non-converters. Hippocampal volume reduction has also been documented in HR and UHR groups (Fusar-Poli et al., 2012; Walter et al., 2012), and has been connected to poor

recall by UHR subjects (Hurlemann et al., 2008). Taken together, these findings are evidence that levels of cognitive impairment increase through the prodromal stages of psychosis.

Neurocognitive function is assumed to influence occupational matters and employment status. It is highly possible that our finding of a strong association between neurocognitive performance and one's level of general functioning is an expression of this. On that account, it has been argued that environmental factors assessed during the initial screening, e.g., being unemployed, should be included in any risk assessment (Koutsouleris et al., 2011). This would be particularly useful because the transition of vulnerability into prodrome and, ultimately, to the point of psychotic crisis, may be triggered by relevant environmental factors (Falkai et al., 2013).

Nevertheless, the brain is a highly flexible and plastic organ that has the ability to change as a result of experience, emotions, and behavior. For example, the deficits seen in at-risk subjects may reflect a temporary expression of psychiatric stress in general rather than a compelling degradation associated with the path to manifestation of a disorder. The HR state is further characterized by a marked impairment in psychosocial functioning (Velthorst et al., 2010), many comorbidities (Yung et al., 2008) and fluctuations in psychiatric symptoms, such that neuropsychological performance may vary. In this study, we assume that we failed to find putative prodrome features that clearly distinguish between early-HR and the at-risk bipolar state because potential impairments associated with psychotic vulnerability might have been too subtle and, thus, were overlaid by other attributes associated with an at-risk state.

Neuropsychological performances differed among our three at-risk groups. Therefore, the previously only on the basis of psychopathological symptoms defined risk classification, was also reflected at the neuropsychological level. Psychomotor deficits, which are primarily unspecific, may have delicately affected the performance of the more complex, higher cognitive functions. Above all, the social and vocational outcomes may have been more strongly influenced by neurocognitive deficits than by psychiatric symptoms. Together with prior evidence, our findings imply that subjects at risk for psychosis already have substantial cognitive deficits. Therefore, to prevent a downward spiral of neurocognitive deficits, educational or occupational crises, and a loss of social embedment that may trigger a transition to psychosis, we believe that practitioners should recognize cognition as a treatment target in itself.

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Declaration of Interest

None.

Contributors

Author 1 wrote the first draft of the article. Authors 1, 2, 3, and 5 collected data. Authors 1 and 4 undertook the statistical analysis. Authors 2, 6, 7, 8, and 9 contributed to the conception of the ZInEP study design. All authors have contributed to and have approved the final manuscript.

Table 1 Demographic and clinical characteristics.

	CG	HR	UHR	HRBip	Test statistics
N	50	75	102	30	
Gender (f:m)	20:30	32:43	39:63	12:18	$\chi^2 = 1.19$, $p = 0.52$
Premorbid verbal IQ, (mean ± SD)	105.94±10.7	103.76±11.0	102.52± 12.9	105.16±11.4	F=1.45, p =0.24
Medication* (mean ± SD)	-	22.89±80	40.42±139	2.12±10	F=1.18, p=0.31
Age (years ± SD)	21.06±5.5	22.94±5.2	19.80±4.8	23.71±6.3	F=11.2, p=0.001
PANSS (mean ± SD), positive	-	10.43(±3.29)	15.26 (±3.85)	8.96(±1.89)	F=75.08, p<0.001
PANSS (mean ± SD), negative	-	11.69 (±4.2)	16.1 (±5.6)	11.34(±4.48)	F=18.58, p<0.001
PANSS (mean ± SD), global	-	27.36(±6.4)	34.56(±6.4)	26.72(±4.8)	F=28.35, p<0.001
GAF (mean ± SD)	-	59.21 (±15.1)	51.9(±12.1)	63.40(±11.3)	F=11.41, p<0.001
HAMD (mean ± SD)	-	13.39 (±6.4)	16.32(±7.8)	11.30(±6.5)	F=7.16, p =0.001
HCL (mean ± SD)	-	18.14 (±4.5)	16.90(±5.6)	15.61(±5.5)	F=2.36, p=0.09
SPI-A/CY, N (%)	-				
Cognitive-perceptive	-	70 (93.3%)	77 (75.5%)	0	
Cognitive disturbances	-	46 (61.3%)	63 (61.8%)	0	
SIPS, N (%)					
Attenuated positive symptoms	-	0	93 (91.2%)	0	
Brief limited intermittent psychotic symptoms	-	0	7 (6.9%)	0	
State–trait criteria	-	0	15 (14.7%)	0	

*Chlorpromazine equivalents.

Table 2 Neurocognitive assessment.

Functional domain	Test	Variable
Premorbid verbal IQ	Vocabulary test: Mehrfachwahl-Wortschatz-Intelligenztest (MWT; Lehrl, 1989); Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn 1981)	Raw score correct
Speed	Trail-Making Test, Version A and B (TMT-A/B; Reitan and Wolfson, 1985)	Time to complete test
	Digit Symbol Coding Test (DSCT; Subtest of WIE; Aster et al., 2006)	Number correct
Attention	Continuous Performance Test (CPT-OX; Beck et al., 1956)	Reaction time, Number of omissions
Learning /Memory	Rey Auditory Verbal Leaning Test (RAVLT; Helmstaedter et al., 2001), Rey Visual Design and Learning Test (RVDLT; Spreen and Strauss, 1991)	T1, ∑T1-T5, Delayed, Recognition
Working Memory	Digit Span and Letter-Number Sequencing (DS and LNS; Subtests of WIE; Aster et al., 2006)	Number correct,
Fluency	Fluency Test, S-Words and Animals (RWT; Regensburger Wortflüssigkeitstest; Aschenbrenner et al., 2000)	Number correct
Planning/Categories	Tower of Hanoi, computerized version (ToH; Gediga and Schöttke, 2006), Wisconsin Card Sorting, 64-card computerized version (WCST; Drühe-Wienholt and Wienholt, 2004)	Time to complete test, Number of moves Perseverative errors

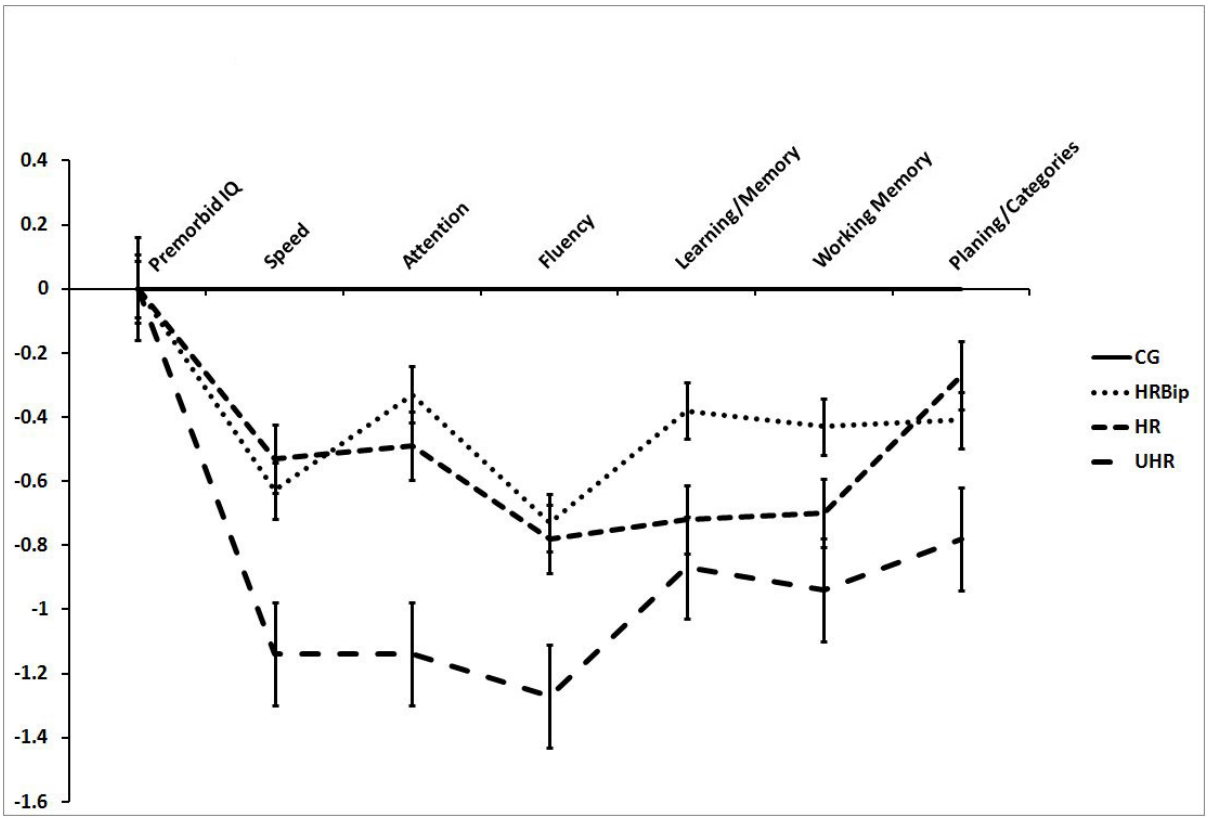

Fig. 1 Mean scores in cognitive domains for 3 at-risk groups (HR, UHR, and HRBip), presented as z-score deficits relative to healthy control group (CG).

Table 3 Test scores and results from one-way ANOVAs of neurocognitive measures.

	CG		HR		UHR		HRBip		Test statistic	
Domain measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	*p*-value
Speed										
TMT_A	21.49	6.1	24.14	6.3	29.76	8.7	26.04	7.66	15.56	<0.001
TMT_B	48.99	12.8	62.85	2.1	63.30	19.0	56.83	14.30	8.53	<0.001
DSCT	83.55	15.0	74.90	15.0	67.48	15.8	75.75	13.40	11.78	<0.001
Attention										
CPT_RT	435.06	71.9	461.92	103.0	482.70	103.1	488.83	120.80	2.91	0.032
CPT_Omis	0.38	0.6	1.00	3.0	2.80	5.2	0.27	0.52	6.84	<0.001
Learning/Memory										
RAVLT_D1	8.90	2.4	7.68	2.4	7.39	2.1	8.23	2.40	18.40	<0.001
RAVLT_Σ1-5	62.40	6.4	56.16	10.0	52.98	11.2	58.70	10.40	17.67	<0.001
RAVLT_Recall	13.76	1.7	11.47	3.2	11.06	2.9	12.33	3.50	10.37	<0.001
RAVLT_WF	14.42	1.7	13.16	3.4	13.27	2.3	13.43	3.20	2.94	0.061
RVDLT_D1	6.12	1.8	5.45	2.2	5.27	2.3	5.90	2.00	1.94	0.120
RVDLT_ Σ1-5	53.26	8.9	49.73	12.0	47.97	11.8	54.40	8.40	4.09	0.007
RVDLT_Recall	13.12	1.7	12.07	3.15	11.78	3.0	13.27	1.40	4.20	0.006
RVDLT_WF	14.58	0.8	14.15	1.1	13.65	1.9	14.60	0.62	6.30	0.001
Working memory										
DS_tot	18.96	3.5	16.88	3.4	15.47	3.3	17.53	4.90	10.34	<0.001
LNS	13.33	2.8	10.57	2.2	10.12	2.8	12.07	3.07	17.29	<0.001
Fluency										
RWT_S-Words	16.76	3.1	13.28	3.7	11.44	3.8	12.93	4.5	22.16	<0.001
RWT_Animals	23.04	2.9	21.43	4.4	19.40	5.1	21.67	5.1	7.98	<0.001
Planning/Categoris										
ToH_mov	55.20	15.7	53.40	17.5	61.53	23.4	63.00	32.3	1.99	0.116
ToH_RT	174.70	68.5	228.3	197.1	267.5	218.0	221.5	146.9	2.31	0.077
WCST_pers	5.49	11.2	6.87	11.8	10.13	11.9	3.23	5.9	3.80	0.011

Note: One-way ANOVA was performed for each measure, using group (CG, HR, UHR, and HRBip) as between-subject factor and age as covariate. Abbreviations for neuropsychological measures are defined in Table 2.

Table 4 Results of logistic regression analysis.

Sample statistics				Model			
Domain	HR	UHR	Converter	UHR vs. HR		Converter vs. UHR/HR	
	Mean±SD	Mean±SD	Mean±SD	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Speed	-0.53±0.8	-1.16±1.0	-1.05±0.8	0.48 (0.28-0.78)	**0.004**	-	
Attention	-0.49±1.1	-1.13±1.3	-0.36±0.6	0.83 (0.60-1.16)	0.272	-	
Learn/Mem	-0.72±1.0	-0.90±0.9	-1.60±1.1	-	-	0.47(0.25-0.87)	**0.017**
Work Mem	-0.70±0.7	-0.98±0.9	-1.15±0.9	1.50 (0.78-2.86)	0.21	-	
Fluency	-0.78±0.9	-1.28±1.0	-1.72±1.0	0.77 (0.47-1.24)	0.283	0.85(0.42-1.74)	0.663
Age	0.39±0.9	-0.41±0.8	-0.11±0.8	0.42 (0.26-0.67)	**0.000**	0.69(0.30-1.58)	0.381

Supplementary Table 1 Factor-loadings in the rotated component matrix (N = 257).

	Component				
	1	2	3	4	5
Measure	Learning / Memory	Working memory	Fluency	Speed	Attention
RAVLT_T1	0.580				
RAVLT_T1-5	0.770				
RAVLT_delrec	0.822				
RAVLT_WF	0.767				
RVDLT_T1	0.639				
RVDLT_T1-5	0.794				
RVDLT_delrec	0.721				
DS_tot		0.924			
DS_span		0.839			
DS_back		0.796			
LNS		0.672			
RWT_1S			0.618		
RWT_2S			0.600		
RWT_1anim			0.814		
RWT_2anim			0.834		
TMT_A				0.682	
TMT_B				0.687	
DSCT				0.423	
CPT_RT					0.757
CPT_omis					0.652

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7 Discussion

The studies presented and enclosed in this work aim both to contribute to a better understanding of the pathophysiological mechanisms of schizophrenia or the prodromal phase of the disease respectively. The two studies emphasize on different time points in the course of the disorder, study I focus on ego-pathology symptoms in manifest schizophrenia, while study II explores the neurocognitive profile of subjects at-risk for psychosis. Both fields studied, self-disturbance and neurocognitive impairments, have the potentials to inherit measures that may function as predictors in assessments related to early detection of psychosis. To create useful tools for risk assessment out of a theoretically assumed self-disturbance in psychosis risk subjects, it seems essential to learn foremost more about the appearance of the symptoms in the manifest and late state. Contrary, the wealth of literature research related to cognition in schizophrenia brought Green (2013) to the statement “It is difficult to wrap one’s arms around an elephant”. Accordingly, in psychosis risk assessments it is already established to screen for neuropsychological impairments to optimize risk prediction. Nevertheless, to create useful intervention in the early stage of the illness, the appearance of neurocognitive deficits still needs to be clarified and remains a highly debated topic. In the next sections the study findings will shortly be summarized and the main results discussed.

7.1 Discussion study I

Study I entitled “Evaluation of trait adjectives and ego pathology in schizophrenia: an N400 study” was designed to investigate the network of self-related reflective self in schizophrenia using the N400 related components in an electrophysiological recording. In controls, the N400 was significantly more negative during processing of incongruent stimuli compared to congruent stimuli. In contrast, patients exhibited no significant amplitude difference between these two conditions. Furthermore, a significant association between the magnitude of patients' N400 effects (difference between incongruent and congruent amplitude) and the severity of their ego-pathology symptoms was observed. In addition, behaviourally, controls but not patients, showed a bias towards shorter reaction time in self- compared to other-reference trials, that is, controls were significantly faster in judging whether adjectives applied to themselves than whether they applied to another person.

The preliminary result of a classic N400 elicited by processing of trait-adjective, specifically by semantic violations of the own self concept, was not often reported before. Watson and collegues (2007) found in similar study protocol the magnitude of the N400 over fronto-central scalp locations to be larger for self-negative words compared to self-positive. Our finding provides evidence that in controls, according to the integration and inhibition theory of the N400, little inhibition was needed to integrate an adjective in a congruent sentence ending (Debruille, 2007). In incongruent sentence

endings more integration was needed which resulted in more inhibitory processes. In patients, a difference in response to incongruent and congruent stimuli could not be observed which lead to the conclusion that the N400 induced by trait adjectives inconsistent with self-referential associative network may be less pronounced in schizophrenia patients with prominent ego-pathologies as the "internal prime" of a stable self-concept (Kircher et al., 2000) is missing. The finding of shorter reaction time to self- than other-related judgments, which could only be observed in controls, may provide additional support for this hypothesis. Additionally, only patients showed a pattern to significantly heightened Yes-answers (independently of valence) in the self-reference condition which may be explained by increased self-attribution in schizophrenia due to above discussed alteration in the attribution of salience (Esslinger et al., 2012). Finally, the clinically most interesting finding of our study is the correlation between the manifestation of ego-pathologies and the N400 effect. This may be interpreted in the way, that there may be a connection between a disordered self-concept (manifested by the existence of ego-pathology symptoms) and the disturbed semantic processing as indexed by the N400 effect. The interpretation of Debruille (2007) may suit to explain the results; he assumes that an integration deficit is responsible for the small N400 in patients and not less intense integration efforts. In schizophrenia patients, the integration deficit may be more pronounced with rising degree of severity of ego-pathology symptoms. Furthermore, it could be speculated that the integration deficit is partly responsible for the persistence of ego-pathology symptoms, which in turn cause a disturbed representation and evaluation of the subject's experiences of the environment.

7.1.1 Benefits and limitations study I

For the realization of study I many obstacles had to be manoeuvred which could not all be avoided and limit the findings of the study. Foremost acquiring suitable and motivated study subjects was found to be very challenging as the schizophrenia patients often suffered from comorbid disorders such as depression, substance abuse or full filled other study exclusion criteria. Other subjects exhibiting the required symptom complex could not be included because cognitive deficits or scarce understanding of German made a thoroughly mastering of the cognitive quite demanding study paradigm unlikely. Due to those reasons the sample size remained relatively small, even though substantial enough to enable statistical power.

Next, the observed smaller or missing N400 effect in schizophrenia may be due to alterations at different points of the information processing system. Deficits in context processing or maintenance as well as verbal working memory decay have been linked with the lack of the N400 effects in schizophrenia (Kostova et al., 2005; Salisbury, 2010; Salisbury, 2008; Sitnikova et al., 2002). Since the context in our experiment is not strictly defined but "needs to be imagined", it is possible that the patients had difficulties fulfilling the experimental task and had problems utilizing the activated

semantic representations of the personal pronouns which indicated the context (self or other-reference) the same way the healthy subjects did. If so, this would have prevented the normal spread of activation in semantic memory networks of the prime concept. An additional and similarly arranged control or baseline condition would have probably clarified this aspect.

Moreover, investigation is needed to differentiate between the phenomenological manifestation of the psychopathological symptoms as well as the cognitive requirement of the self-referential tasks. Strictly speaking, the task operationalized the reflective self as suggested by Esslen et al. (2008) while theoretical assumptions suggest that the self in schizophrenia is disordered at the more basic, pre-reflective self (Nelson et al., 2008). However, it is possible that while being in a reflective self-reference by reflecting on one's own traits, processes related to pre-reflective self may co-occur. That is, the mental flow, when engaged in higher level self-consciousness may involve a rapid change from the pre-reflective first-person perspective to the reflective third-person perspective (Esslen et al., 2008). Moreover, as Maj (2012) critically stated, the approach explaining self-disturbance through failures on level of pre-reflective self (e.g. Parnass and Handest, 2003) are rather suited to explain abnormalities *before* the onset of psychosis, while it may be assumed that reflective and narrative self are delicately altered *after* a conversion to psychosis and the struggling of the individual with more or less remaining symptoms. Nevertheless, this study tried to focus exploratory on a newly aspect of N400 in schizophrenia, giving rise to new questions and ideas. Certainly, further studies performed with a larger sample size and additional control conditions are necessary to confirm the findings of the study.

7.2 Discussion study II

This study analyses the neurocognitive performance of three groups of subjects at risk for schizophrenic or affective psychosis and examined whether those psychopathological defined risk groups can be distinguished by performance on neuropsychological domains. The main findings were as follows: First, the three at-risk groups were impaired relative to the control group on all domains in the way that the HR and HRBip were performing both at a comparable and intermediate level between controls and UHR. Second, among subjects at-risk of psychosis, performance in speed domain predicted a group affiliation of UHR while learning and memory deficits predicted a transmission to psychosis. Third, neuropsychological deficits had a profound effect on level of general functioning and general satisfaction with life.

Our findings were consistent with previous studies examining individuals comparable to our UHR subjects (Hawkins et al., 2004; Eastvold et al., 2007; Brewer et al., 2005; Pflueger et al., 2007; Lencz et al., 2006) and studies which showed moderate deficits in subjects with basic symptoms (Frommann et al., 2011; Pukrop et al., 2006; Simon et al., 2007). Our group of at-risk bipolar subjects exhibited a

quantitatively similar profile to the HR psychosis subjects, that is, we failed to find putative prodrome features that clearly distinguished between HR and HRBip. Our findings further support the hypothesis of processing speed independently of medication as central deficit associated with increased risk for psychosis (Kelleher et al., 2012, Riecher-Rössler et al., 2013), and further that this neurocognitive domain might represent an additional predictive marker that should be included in multilevel assessments of psychosis risk proneness.

By means of theoretical considerations Goldman-Rakic (1994) postulated a working memory dysfunction as central supramodal disturbance in cognition of schizophrenia which is independent of a possible general cognitive deficit. It is assumed to influence most of upward connected executive processes and may explain most of psychopathology in schizophrenia such as disordered goal directed and adaequate behavior, deficits in the sequential planning of actions and decisions or desorganised cognition and characteristic formal thought disorder (Wolf and Walter, 2008). In line with this, the meta-analysis of De Herdt (2013) found the performance in the domains of working memory and visual learning in clinical psychosis high risk subjects who later converted to psychosis to be significantly more impaired than in non-converter. In our sample the converters were in fact, and comparable to the finding of the meta-analysis, distinguished at the baseline assessment by their poor result in learning and memory domain, but we could not corroborate the special deficit in working memory compared the other at-risk non-converter. On the one hand, small effect sizes might account for these conflicting results, on the other, possible differences in test selection for the operationalization of the working memory domain.

Generally, executive functions are thought to serve the coordination, controlling and timing of different subprocesses in the brain (Eliott, 2003). Accordingly, various processes are accounted to executive functions: inhibition, monitoring, cognitive flexibility, planning and problem solving. Due to this a precise definition of which subprocess investigated is necessary to avoid inconsistency in findings. Evidence regarding deficits in schizophrenia patients in the performance on single tests as for instance the Wisconsin Card Sorting Test, a measure of cognitive flexibility and set shifting (WCST; Grant and Berg, 1948) (e.g. Weinberger et al., 1994) or the Tower of London (Shallice, 1982; Tower of Hanoi as computerized version) as measure of planning and problem solving have been repeatedly reported (e.g. Rasser et al., 2005). Our study found significant group differences on the performance of the computerized version of the WCST and ToH, however the single measures were not used for further analysis in the regression models as in factor analysis they exhibited high cross loadings on most factors.

A more promising way to study the performance and neuronal correlate of executive function in schizophrenia and psychosis high risk states seems to be the analysis of the connectivity and interaction of prefrontal cortex regions with other brain areas. Likewise, we found in the identical at-

risk psychosis sample of the ZInEP study the inter-network-connectivity of the default mode with the task positive network to be significantly associated with the time to solve the problem of the Tower of Hanoi task. In addition, with increasing complexity of the problem (four disk to five disk tower), the association turned out to be stronger (Wotruba et al., accepted). Therefore it may be concluded that the active inner mental operations needed to solve the tasks are only successful achieved if the continuously incoming stream of external stimuli is sufficiently suppressed which in turn is regarded as core central deficit in schizophrenia (Goldman-Rakic 1994). The cognitive deficit thus seen in the at-risk psychosis subjects of the ZInEP study may be linked to a loss of antagonism in task positive and default mode network. This network is thought to reflect the competition between external and internal information processing, and, as proposed by Wotruba et al. (accepted), this may trigger a confusion of internally and externally focused states and with that a vulnerability to psychotic reality distortion.

7.2.1 Benefits and limitations study II

The HR state is characterized by marked impairment in psychosocial functioning (Velthorst et al., 2009), many comorbidities (Yung et al., 2008) and by fluctuations of psychiatric symptoms, and with that, neuropsychological performance may vary. Our evidence concerning prediction of group affiliation to the early HR or more ill putative UHR group is thus limited because of the cross-sectional analysis of baseline assessment data. The deficits seen in the at-risk subjects thus may reflect a temporarily expression of psychiatric stress in general rather than a compelling degradation associated with the path to manifestation of the disorder. A 2%- (van Os et al., 2009) up to 8%-rate (Schimmelmann et al., 2011; Kelleher et al., 2012) of psychotic-like experiences in general population has further been discussed depending on which time criteria are implemented, and whether psychosocial function deficits are implicated as inclusion criteria.

The neuropsychological impairments further could be an expression of depressive symptoms. However we carefully controlled for this confounding variable and the effects still were observable. We tried to align our neurocognitive assessment to the suggestion of the MATRICS consensus test battery (Green and Nuechterlein, 2004) however our battery is not directly comparable to their suggestion due to several project specific issues like the need for using established tests in German language. Moreover the selection of test variables and their assigning to domains (eg. memory, distinction verbal and non-verbal material) always gives a certain leeway so that the comparability between studies always needs carefully to be verified.

7.3 General Discussion

A common denominator of the two studies is the aim to contribute to a better understanding of the pathophysiological mechanisms of schizophrenia. With increased interest in the pre-onset phase of psychotic disorders and with the aim to find biological markers of risk and thus optimizing risk prediction, research has recently begun to study phenomenological and neural anomalies reflecting a basic self-disturbance in psychosis risk subjects while in the domain of neurocognition it is already a long tradition. It is challenging to study schizophrenia patients who have been ill for a prolonged time, because it is difficult to disentangle the effects of ongoing illness, treatment or other complications such as substance use. However, a newly task to measure the organization in the network of self-related reflective self in schizophrenia using the N400 related components has been introduced. The Examination of Anomalous Self Experience and the Schizophrenia Proneness Instrument are seen as promising tools to investigate subjectively experienced self-related alterations in perception and thought reported by help-seeking at risk psychosis subjects (Nelson, 2008). However, for being able to answer correctly the questions on quite complex and subtle alterations in perception and thought implemented in the interviews differentiated verbal skills is a requirement on the one hand and on the other, good introspection as well as motivation to go on through the long assessment. In a planned analysis it is intended to investigate the association of self-reported alterations in cognition (rated on the SPIA) and objective performance in neurocognition in the ZInEP at-risk sample with other measures of introspection to clarify this assumption.

As specified in section II the ego-pathology symptoms seen in schizophrenia are thought to be related to deficits in self-monitoring and aberrant salience. Self-monitoring involves executive function and online monitoring such as working memory processes (Frith and Friston, 1998). However, the relationship between neurocognitive deficits measured by traditional neuropsychological tests and self-monitoring functions is still unclear. Schizophrenia patients show deficits in both working memory and executive function. One study could show that in healthy controls the performance in both domains was highly correlated, whereas in schizophrenia working memory and executive dysfunction was only related to deficits in retrieval of episodic memory (Boeker et al., 2006). Positive and negative symptoms were not directly related to the working memory and executive dysfunction while ego-pathology was. The authors concluded that because of both, deficits in and functional dissociation between working memory and executive function the patients may be no longer able to experience and monitor self-related processes. It is thus essentially a failure in cohesion in self-related processes which may result in delusions of alien control that reflect ego-pathology (Boeker et al., 2006).

7.4 Conclusion

Several decades of research into schizophrenia has created a plethora of studies related to the phenotypic nature of the disturbance and its distinct cognitive features. The enclosed studies have been conducted representing different theoretical approaches and at different stages of the course of the illness to investigate the underlying pathomechanisms. Due to the heterogenous manifestation of psychopathological symptoms arising from the complex and multifaceted disorder schizophrenia it is a challenge to clarify all the open questions and unravel the exact neuronal disorder. To date it is most accepted that a distinct cognitive decline is already measurable in individuals at risk for the disorder and our data do support this approach. Based on the evidence provided by our studies we conclude that by all means a neurocognitive assessment should be included in an initial psychosis risk assessments firstly, to prevent a downward spiral of neurocognitive deficits, educational or occupational crisis and loss of social embedment that may trigger a transition to psychosis and secondly, because neurocognition may inherit a potential to ameliorate psychosis risk prediction. More research is needed to clarify which benefits and potential disadvantages, like stigma associated stress, are involved with a labeling of being at-risk of psychosis (Yung et al., 2012; Ruesch et al., submitted). This is an issue, which was also conversely discussed in the context of the debate about introducing a new attenuated psychosis syndrome as diagnostic category in the DSM-V (Fusar-Poli et al., 2013). Furthermore, if forthcoming research confirms the core phenotypic nature of self-disturbance in schizophrenia and in clinical high risk states, then it is necessary address this in psychological treatment (Nelson et al., 2013). A therapeutic approach using body oriented psychological therapies may be more promising in individuals suffering a hyper-reflexive attitude, than cognitive behavioral therapy, in which individuals are encouraged to “think about thinking”(Nelson et al., 2013). Hopefully, the longitudinal clinical and neuropsychological data of the ZInEP study will contribute to further clarify whether different patterns of cognitive impairment predict psychosis in early or late prodromal stages. Nevertheless, further research is still needed to gain more information about manifestation of self-related disturbance and cognition in the different stages of the course of the illness.

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Curriculum Vitae

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Date of Birth	August 12, 1979
Place of Birth	Balgach, Switzerland

Education

2000 – 2006	Master of Science in Psychology, University of Zurich

Employments

03/2013 – current	Psychologist, Psychiatric University Hospital Zurich, out-patient treatment, Department of Psychiatry, Psychotherapy and Psychosomatics, Switzerland
11/2009 – current	Psychologist, Psychiatric University Hospital Zurich, The Zurich Program for Sustainable Development of Mental Health Services (ZInEP), Switzerland
03/2008 – 12/2010	Psychologist, Psychiatric University Hospital Zurich, inpatient treatment, Department of Psychiatry, Psychotherapy and Psychosomatics, Switzerland

Clinical Traineeships

09/2007 – 12/2007	Special Needs Department, Dolphin Research Center, Marathon (USA)
11/2004 – 12/2004	Psychiatric Hospital Solothurn
09/2003 – 01/2004	Neuropsychological traineeship at Dr. phil. E. Hinder, Uster

Research Projects

2005	Participation and implementation of experiment “Mental own-body and body-part transformations in microgravity” on the regular Parabolic Flight Campaign.
2004	Participation on the 7th ESA student Parabolic Flight Campaign of European space agency.

List of publications

Publications in peer-reviewed journals

Wotruba, D., Michels, L., Buechler, R., **Metzler, S**., Theodoridou, A., Walitza, S., Kollias, S., Rössler, W., Heekeren, K. (accepted). Aberrant coupling within and across the default-mode, task-positive, and salience network in subjects at risk for psychosis. *Schizophrenia Bulletin*

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Disorders and Coherence of the Embodied Self (DISCOS), Heidelberg (2008).”Pre-reflective and reflective self-reference in schizophrenia”. **Metzler, S.**, Heekeren, K., Hoff, P., Theodoridou, A.

International Symposium Brain Electrophysiology Congress (ISBET), Bern (2005). “Pre-reflecitve and reflective self-reference: a spatiotemporal EEG analysis. Esslen, M., **Metzler, S.**, Pascual-Marqui, R., Jancke, L.